PTO/SB/21 (01-08)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	50

Application Number	09/338,185; Patent No. 6,403,567
Filing Date	22 Jun 1999; Issued 11 June 2002
First Named Inventor	Jeff Zablocki
Art Unit	1623
Examiner Name	CRANE, LAWRENCE E.
Attorney Docket Number	99-0423

ENCLOSURES *(Check all that apply)*

- [X] Fee Transmittal Form
- [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [X] Other Enclosure(s) (please Identify below):

Application for Extension of Patent Term Under 35 USC 156 (Original plus 2 copies)

Remarks

RECEIVED
JUN 06 2008
PATENT EXTENSION
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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	CV Therapeutics, Inc.		
Signature			
Printed name	Daniel W. Collins		
Date	June 6, 2008	Reg. No.	31,912

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being ~~facsimile transmitted to the USPTO~~ or deposited with the United States Postal Service with sufficient postage as ~~first class mail~~ in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below: ^ Express Mail - Mail Stop Hatch-Waxman PTE

Signature			
Typed or printed name	Marjory Darrow	Date	06/06/2008

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and1.14. This collection is estimated to 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/SB/17 (10-07)
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Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2008

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,120.00

Complete if Known	
Application Number	09/338,185; Patent No. 6,403,567
Filing Date	22 Jun 1999; Issued 11 June 2002
First Named Inventor	Jeff Zablocki
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Art Unit	1623
Attorney Docket No.	99-0423

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JUN 06 2008
PATENT EXTENSION
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METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 50-1789 Deposit Account Name: CV Therapeutics, Inc.

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	310	155	510	255	210	105	
Design	210	105	100	50	130	65	
Plant	210	105	310	155	160	80	
Reissue	310	155	510	255	620	310	
Provisional	210	105	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	210	105
Multiple dependent claims	370	185

Total Claims		Extra Claims	Fee ($)	Fee Paid ($)
_____	- 20 or HP =	_____	x _____	= _____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims	Fee ($)	Fee Paid ($)
_____	- 3 or HP =	_____	x _____	= _____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____	- 100 =	_____	/ 50 =	_____ (round up to a whole number)	x 260.00	= 0.00

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): Hatch-Waxman - Patent Term Extension	1,120.00

SUBMITTED BY

Signature	[signature]	Registration No. (Attorney/Agent) 31,912	Telephone 650-384-8671
Name (Print/Type)	Daniel W. Collins		Date June 6, 2008

This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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FEE TRANSMITTAL
For FY 2008

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,120.00

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METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 50-1789 Deposit Account Name: CV Therapeutics, Inc.

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

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☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

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	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
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Each independent claim over 3 (including Reissues)	210	105
Multiple dependent claims	370	185

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____ - 20 or HP =	_____ x	_____ =	_____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____ - 3 or HP =	_____ x	_____ =	_____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
_____	_____

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Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____ - 100 =	_____ / 50 =	_____ (round up to a whole number) x	260.00 =	0.00

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): Hatch-Waxman - Patent Term Extension	1,120.00

SUBMITTED BY

Signature	[signature]	Registration No. (Attorney/Agent) 31,912	Telephone 650-384-8671
Name (Print/Type)	Daniel W. Collins		Date June 6, 2008

This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re:	US Patent No. 6,403,567
Issued:	June 11, 2002
Application No:	09/338,185
Filed:	June 22, 1999
Inventors:	Zablocki et al.
Assignee:	CV Therapeutics, Inc.
For:	N-pyrazole A_{2A} adenosine receptor agonists

Mail Stop Hatch-Waxman PTE
Director of the United States Patent and Trademark Office
PO Box 1450
Alexandria, Virginia 22331-1450

Application for an extension of patent term under 35 USC 156

CV Therapeutics, Inc., a Delaware corporation, is the assignee of the entire interest in US Patent No. 6,403,567 issued on June 11, 2002, for N-pyrazole A_{2A} adenosine receptor agonists, by an assignment from the inventors, Zablocki et al., to CV Therapeutics, Inc. recorded on August 16, 1999, at Reel 010187, Frame 0341.

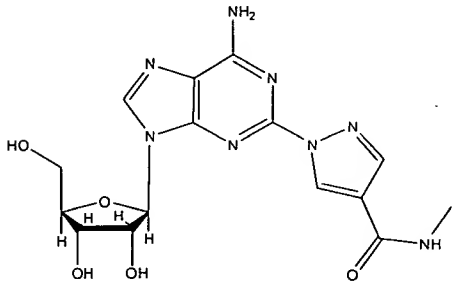
CV Therapeutics, Inc. hereby requests an extension of the patent term of US Patent No. 6,403,567 by stating that the regulatory review period has been completed, and by providing the following information, as required by 35 USC 156 and 37 CFR 1.710.

1. Complete identification of product

The product recently approved by the US Food and Drug Administration is Lexiscan™ regadenoson 0.4 mg/5 mL injectable solution.

It comprises a compound having:

(a) the structural formula:



(b) the molecular formula: $C_{15}H_{18}N_8O_5$;

(c) the molecular weight: 390.35;

(d) the chemical names:

(1) adenosine, 2-[4-[(methylamino)carbonyl]-1*H*-pyrazol-1-yl]-; and

(2) 1-[6-amino-9-[(2R,3R,4S,5R)-3,4-dihydroxy-5- (hydroxymethyl)oxolan-2-yl]purin-2-yl]- N-methylpyrazole-4-carboxamide; and

(3) (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide [from US Patent Application No. 09/338,185 e.g. at Example 5, page 27, lines 6-7]; and

(4) 2-(4-methylaminocarbonylpyrazol-1-yl)adenosine [from US Patent No. 6,403,567 e.g. at claim 7].

(e) the generic names:

(1) regadenoson (monohydrate) (USAN), and

(2) regadenoson (monohydrate) (INN); and

(f) the CAS registry numbers:

(1) 313348-27-5 (free base); and

(2) 875148-45-1 (monohydrate).

2. Identification of Federal statute/provision of law

Lexiscan ™ (regadenoson 0.4 mg/5 mL injectable solution), was subject to regulatory review under Section 505(b) of the Federal Food, Drug and Cosmetic Act.

3. Date on which product received permission for commercial marketing or use

Lexiscan ™ (regadenoson 0.4 mg/5 mL injectable solution), received permission for commercial marketing under Section 505 (b) of the Federal Food, Drug and Cosmetic Act on April 10, 2008.

4. Identification of active ingredient

Lexiscan ™ (regadenoson 0.4 mg/5 mL injectable solution), contains as its sole active ingredient regadenoson monohydrate, which in solution is converted to free base, described above in item 1. This product has not previously been approved for commercial marketing under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act.

5. Time period for submitting application

This application for extension of patent term is being submitted within the sixty day period permitted for submission pursuant to Section 37 CFR 1.720 (f). The date of FDA approval was April 10, 2008. The submission period begins on April 10, 2008, and ends on June 8, 2008.

6. Identification of patent

The patent for which patent term extension is being sought is US Patent No. 6,403,567 inventors Zablocki et al., which issued on June 11, 2002, for N-PYRAZOLE A_{2A} ADENOSINE RECEPTOR AGONISTS. The term of US Patent No. 6,403,567 will expire, unless extended again, on June 22, 2019.

7. Copy of patent

A copy of US Patent No. 6,403,567 is attached as Attachment A.

8. Other patent documents

A copy of the Certificate of Correction which issued with respect to US Patent No. 6,403,567 is attached as Attachment B.

Notice of Recordation and assignment from the inventors to CV Therapeutics, Inc. is attached as Attachment C.

No disclaimer or Reexamination Certificate has issued with respect to US Patent No. 6,403,567.

9. Claims covering the product

US Patent No. 6,403,567 claims Lexiscan™ (regadenoson 0.4 mg/5 mL injectable solution), in the following applicable claim:

Claims 1- 4 cover regadenoson free base when

R^3 is $CONR^7R^8$, R^7 is methyl, and R^8 is hydrogen.

Claim 5 covers regadenoson free base when

R^3 is $CONR^7R^8$, and R^8 is hydrogen.

Claim 7 covers regadenoson free base [**2-(4-methylaminocarbonylpyrazol-1-yl)adenosine**].

Claim 8 covers regadenoson free base as

R^1 is $-CH_2OH$, R^3 is $CONR^7R^8$, R^7 is methyl, and R^2, R^4, and R^8 are hydrogen.

Claim 9 covers the pharmaceutical formulation Lexiscan™ when

R^3 is $CONR^7R^8$, R^7 is methyl, and R^8 is hydrogen,

and when the formulation contains a pharmaceutically acceptable excipient such as propylene glycol.

Claim 10 covers the pharmaceutical formulation Lexiscan™ when

R^3 is $CONR^7R^8$, R^7 is methyl, and R^8 is hydrogen,

and when the formulation is in the form of a solution and contains a pharmaceutically acceptable excipient such as propylene glycol.

Claims 11 and 13 cover the use of regadenoson free base for use in stimulating coronary vasodilation in a mammal for purposes of imaging the heart when

R^3 is $CONR^7R^8$, R^7 is methyl, and R^8 is hydrogen.

10. Relevant dates and information pursuant to 35 USC 156(g)

The relevant dates and information under 35 USC 156(g) and 37 CFR 1.740(10)(i) are as follows:

August 2, 2001:	Effective date of IND 62,862;
May 14, 2007:	Submission date of NDA 22-161.
April 10, 2008:	Approval date of NDA 22-161.

11. Brief description of significant activities

A brief description of the activities undertaken during the regulatory review period follows.

Submission No.	Date	Content
IND 62,862	6/29/01	Submission of IND application
IND 62,862	7/10/01	Acknowledgement of receipt of IND application
IND 62,862	7/13/01	Fax submission of additional CMC information
IND 62,862	8/24/01	Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use: (Print Press Release)
IND 62,862	8/28/01	Submission of investigator information in CVT 5121
IND 62,862	10/24/01	Submission of amended protocol CVT 5121
IND 62,862	11/20/01	Fax from FDA containing nonclinical comments
IND 62,862	12/13/01	Submission of investigator information in CVT 5121
IND 62,862	1/10/02	Submission of investigator information in CVT 5121
IND 62,862	1/18/02	Voicemail regarding change in CVT contacts for projects
IND 62,862	1/31/02	Submission of change in primary contact for IND 62,862
IND 62,862	2/6/02	Submission of investigator information in CVT 5121
IND 62,862	4/5/02	Submission of investigator information in CVT 5121
IND 62,862	5/3/02	Fax submission of meeting request
IND 62,862	5/10/02	Fax meeting request and list of questions
IND 62,862	5/21/02	Fax from FDA confirming meeting
IND 62,862	5/29/02	Submission of faxed meeting request and list of questions
IND 62,862	7/3/02	Submission of clinical development plan package
IND 62,862	7/23/02	Fax list of CVT meeting attendees
IND 62,862	7/26/02	Minutes from 26 Jul 02 meeting
IND 62,862	7/29/02	Submission of change in authorized representative for IND 62,862
IND 62,862	7/30/02	Submission of new protocol CVT 5122; submission of investigator information in CVT 5121; submission of copy of fax dated 7/23/02
IND 62,862	8/7/02	Submission of CMC information
IND 62,862	8/21/02	Submission of investigator information in CVT 5122
IND 62,862	8/22/02	Fax regarding overheads used by CVT for the presentation at the 26 Jul 02 meeting
IND 62,862	8/28/02	Fax regarding overheads used by CVT for the presentation at the 26 Jul 02 meeting. Resent, as one overhead was not sent in the facsimile dated 22 Aug 02.
IND 62,862	9/4/02	Submission of CMC information
IND 62,862	9/11/02	Submission of Initial Written Report for study CVT 5122
IND 62,862	9/19/02	Submission of investigator information in CVT 5121, and CVT 5122; submission of copy of CVT facsimile dated 28 Aug 02: Presentation overheads at 26 Jul 02 meeting.
IND 62,862	9/23/02	Minutes of a voicemail regarding new CSO, Russell Fortney
IND 62,862	9/24/02	Submission of 1st Annual Progress Report
IND 62,862	10/4 & 9/02	Letter from FDA re 30 Jul 02 protocol
IND 62,862	10/9/02	Fax of FDA meeting minutes of 26 Jul 02
IND 62,862	10/16/02	Submission of investigator information in CVT 5121
IND 62,862	11/13/02	Submission of investigator information in CVT 5121 and CVT 5122
IND 62,862	12/16/02	Submission of protocol amendment to CVT 5121; submission of protocol amendment to CVT 5122; submission of investigator information in CVT 5122
IND 62,862	2/5/03	Submission of investigator information in CVT 5121

Submission No.	Date	Content
IND 62,862	4/2/03	Submission of protocol amendment to CVT 5122
IND 62,862	4/14/03	Submission of Follow-Up Written Report for study CVT 5122
IND 62,862	4/25/03	Submission response regarding mouse bone marrow micronucleus assay
IND 62,862	5/2/03	Submission request for FDA End-of-phase II meeting
IND 62,862	5/2/03	Fax requesting a meeting
IND 62,862	5/8 & 9/03	Voicemail regarding tentative date selected for End of Phase 2 meeting
IND 62,862	5/12/03	Fax confirming End of Phase 2 meeting
IND 62,862	5/13/03	Phone inquiry as to if Imaging Division representatives should be included in the EOP2 meeting
IND 62,862	6/16-17/03	Voicemail requesting twenty copies of the End of phase 2 briefing package
IND 62,862	6/17/03	Submission of information amendment; submission of reports 3003-004P, 3003-004, 3003-005P, and 3003-005
IND 62,862	6/20/03	Submission regarding End of Phase 2 meeting information package
IND 62,862	7/8/03	Voicemail regarding questions for the 11 Jul 03 meeting
IND 62,862	7/9/03	Email regarding list of FDA meeting attendees
IND 62,862	7/11/03	Minutes-CVT: CVT 3146 End of Phase 2 Meeting
IND 62,862	7/18/03	Phone, feedback on the use of radionuclide in the Phase 3 study
IND 62,862	7/23-24/03	Phone regarding dual isotope protocol acceptable; teleconference date to be determined.
IND 62,862	7/25/03	Fax of FDA End of Phase 2 meeting minutes of 11 Jul 03
IND 62,862	7/30/03	Fax regarding teleconference information for 31 Jul 03
IND 62,862	7/31/03	Teleconference follow-up to the 11 Jul 03 EOP2 meeting
IND 62,862	8/5-6/03	Email regarding teleconference arrangements, list of teleconference participants, and request for electronic copies of references
IND 62,862	8/6/03	Teleconference minutes between CVT, FDA, and University of Alabama
IND 62,862	8/7/03	Fax of FDA minutes of 31 Jul 03, and 06 Aug 03 teleconferences
IND 62,862	8/12/03	Fax of corrected FDA minutes of 06 Aug 03 teleconference
IND 62,862	9/4/03	Fax of proposed analysis plan for secondary endpoints in CVT 5131, and complete analysis plan from CVT 5131
IND 62,862	9/9/03	Fax regarding AT & T teleconference information for 12 Sep 03
IND 62,862	9/12/03	Teleconference discussion of analysis of secondary endpoints
IND 62,862	9/16/03	Submission of information amendment to CVT 3146; submission of reports 0793-7771, 0794-7771, 124-021, 124-022, 124-023, and 124-020
IND 62,862	9/26/03	Fax of FDA teleconference minutes of 12 Sep 03, discussion of analysis of secondary endpoints
IND 62,862	10/1/03	Submission of protocol amendment to CVT 5131, and transfer of obligations to CROs
IND 62,862	10/24/03	Submission of investigator information in CVT 5131
IND 62,862	10/30/03	Submission of 2nd Annual Progress Report
IND 62,862	11/26/03	Submission protocol amendment to CVT 5131; submission of investigator information in CVT 5131, and CVT 5121; submission of CVT faxes
IND 62,862	1/7/04	Submission of investigator information to CVT 5131
IND 62,862	1/21/04	Submission of statistical analysis plan for CVT 5131; submission of CVT 5131 Mockup Tables, Figures, and Listings
IND 62,862	2/3/04	Submission of protocol amendment to CVT 5131; submission of investigator information in CVT 5131
IND 62,862	2/6/04	Submission of new protocol CVT 5132; submission of transfer of obligations to CROs for CVT 5132; submission of CMC information
IND 62,862	2/12/04	Phone follow-up
IND 62,862	2/27 & 3/2/04	Email regarding review of the Statistical Analysis Plan, the Pulmonary Division still has not finished with the questions regarding the COPD/asthma study

Submission No.	Date	Content
IND 62,862	3/3/04	Submission of investigator information to CVT 5131
IND 62,862	3/3 & 9/04	Email regarding reference nos. 43, 44, 45, and 47 from the briefing package (11 Jul 03 meeting) sent to FDA as requested
IND 62,862	3/11/04	Email regarding no comments for submissions 034 and 036 from Dr. Hung, and still awaiting on comments from the Pulmonary Division
IND 62,862	3/31/04	Submission protocol amendment to CVT 5121; submission of investigator information to CVT 5131
IND 62,862	3/31/04	Email response from the Pulmonary Division on COPD/asthma study design from the 11 Jul 03 meeting
IND 62,862	4/14/04	Submission protocol amendments to CVT 5131 and CVT 5132
IND 62,862	4/19/04	Submission request for End-of-Phase 2 Meeting to discuss CMC aspects of regadenoson development program, and to review the toxicology studies conducted for the program
IND 62,862	4/19/04	Fax copy of cover letter (#0040): Request for End-of-Phase 2 Meeting
IND 62,862	4/26/04	Email confirmation of Type B Meeting (End of Phase 2) for 18 Jul 04
IND 62,862	4/28/04	Submission of investigator information to CVT 5131; submission of investigator information to CVT 5132
IND 62,862	5/4-6/04	Voicemail and phone conversation regarding Dr. Stockbridge not attending the EOP2 meeting, request of a copy of the briefing materials for the two pharmacology reviewers, and draft questions and toxicology section for pharmacology reviewers sent via fax
IND 62,862	5/5/04	Fax of draft Information Package of 18 May 04 for Pharmacology/Toxicology reviewers
IND 62,862	5/10/04	Submission of Information Package for the 18 May 04 End of Phase 2 Meeting
IND 62,862	5/13/04	Phone call notifying CVT that one FDA chemist will not be able to attend the 18 May 04 meeting, rescheduling of EOP2 meeting will not be necessary
IND 62,862	5/14/04	Fax requesting for FDA feedback on the proposal to modify ECG measurements for protocols CVT 5131 and CVT 5132
IND 62,862	5/18/04	Minutes-CVT: CVT-3146 End of Phase 2 Meeting
IND 62,862	5/24, 6/24, 6/14-17/04	Phone and voicemail regarding storage configurations to be used in CVT's stability protocols for sterility and endotoxin test samples
IND 62,862	5/26/04	Submission of investigator information to CVT 5131 and CVT 5132; submission of technical report 1491/CVT/01-B
IND 62,862	6/1/04	Voicemail regarding status of FDA review/response on CVT's ECG proposal sent by fax, feedback from the FDA microbiologist on the adequacy of the 15-minute sterilization cycle, outcome of discussion on the adequacy of the toxicology qualification studies conducted
IND 62,862	6/2/04	Email agreement on proposal to modify the ECG measurements in protocols CVT 5131 and CVT 5132
IND 62,862	6/3-4/04	Email request for information regarding the toxicology qualification studies conducted
IND 62,862	6/4/04	Voicemail regarding information in the EOP2 briefing package
IND 62,862	6/4/04	Fax requesting feedback on revised clinical study design to evaluate the effect of caffeine on CVT-3146-induced increase in coronary blood flow
IND 62,862	6/15/04	Phone FDA requesting for information regarding the drug substance lots used in the 28-day toxicology study
IND 62,862	6/17/04	Minutes-FDA (Email): FDA End of Phase 2 Meeting Minutes of 18 May 04
IND 62,862	6/18, 6/21-22/04	Email request and confirmation of teleconference for 04 Aug 04

Submission No.	Date	Content
IND 62,862	6/21/04	Submission of investigator information in CVT 5131 and CVT 5132; submission of technical reports 6892-108, AA89JT.503.BTL, CVT3146.053-P: submission of faxes requesting feedback
IND 62,862	6/21/04	Submission request for teleconference to discuss CMC information
IND 62,862	6/21/04	Fax copy of cover letter (#0045): Request for teleconference
IND 62,862	6/23/04	Email confirmation of teleconference for 04 Aug 04
IND 62,862	6/24/04	Email timing for teleconference briefing package and clinical reviewer for ECG question and caffeine study
IND 62,862	6/30/04	Phone comments on Caffeine Study (CVT 5123) Synopsis
IND 62,862	7/1/04	Minutes-CVT (Teleconference): Discussion of Caffeine Study (CVT 5123) Synopsis
IND 62,862	7/2/04	Submission of protocol amendments in CVT 5131 and CVT 5132
IND 62,862	7/14/04	Email regarding Microbiologist comment on sterilization cycle
IND 62,862	7/23/04	Submission of Information Package for 04 Aug 04 Teleconference
IND 62,862	7/30/04	Submission of new protocol CVT 5112; submission of investigator information in CVT 5131 and CVT 5132
IND 62,862	8/5/04	Minutes-CVT: Discussion of impurity
IND 62,862	8/13/04	Phone regarding comments on Protocol CVT 5112 – Renal Study
IND 62,862	8/16/04	Minutes-FDA (Email): Meeting minutes of 05 Aug 04 teleconference
IND 62,862	8/18/04	Submission of investigator information in CVT 5131 and CVT 5132
IND 62,862	8/24/04	Submission of new protocol CVT 5123
IND 62,862	9/2/04	Letter regarding Protocol CVT 5123
IND 62,862	9/7/04	Email of letter regarding Protocol CVT 5123
IND 62,862	9/13, 9/17, 9/21/04	Phone discussion regarding FDA recommendation in the 02 Sep 04 letter that caffeine use not be restricted in the efficacy trails, and clarification regarding Dr. Peter Hinderling's review of Protocol CVT 5123
IND 62,862	9/15/04	Phone request for references for Protocol CVT 5123
IND 62,862	9/16/04	Submission of investigator information in CVT 5131 and CVT 5132
IND 62,862	9/17/04	Submission response to FDA request for copies of references cited in Protocol CVT 5123
IND 62,862	9/27/04	Submission of protocol amendment to CVT 5112
IND 62,862	9/29/04	Email regarding Caffeine Interaction Study response status
IND 62,862	10/5/04	Submission of Request for Waiver of Pediatric Studies
IND 62,862	10/11/04	Submission of 3rd Annual Progress Report: 01 Jun 03 – 31 May 04
IND 62,862	10/12/04	Letter regarding review of Protocol CVT 5123 (#0050) completed, with comments and recommendations
IND 62,862	10/13/04	Email new letter (12 Oct 04) regarding the caffeine study (CVT 5123/#0050): Comments and recommendations
IND 62,862	10/22/04	Letter granting the pediatric waiver
IND 62,862	10/25/04	Email of letter (22 Oct 04) granting the pediatric waiver
IND 62,862	10/28/04	Submission of investigator information in CVT 5131 and CVT 5132
IND 62,862	11/12/04	Submission response to the 12 Oct 04 letter from the Division containing comments and recommendations concerning proposed Study CVT 5123
IND 62,862	11/17-18/04	Email follow-up to review of response on Protocol CVT 5123
IND 62,862	11/19/04	Email of teleconference confirmation (10 Dec 04) to discuss caffeine interaction protocol (CVT 5123)
IND 62,862	11/24, 11/26/04	Email regarding teleconference re-scheduled for 14 Dec 04
IND 62,862	12/8-9/04	Email follow-up on teleconference to discuss the caffeine study, and comment from FDA internal meeting
IND 62,862	12/13/04	Submission of new protocol CVT 5124
IND 62,862	12/14/04	Minutes-CVT: Discussion of any additional comments from the Agency on the protocol (CVT 5123) after their review of CVT's responses

Submission No.	Date	Content
IND 62,862	12/16/04	Submission of investigator information in CVT 5112, CVT 5131, CVT 5132, and transfer of obligation to a CRO for Study CVT 5112
IND 62,862	12/17/04	Phone regarding Protocol CVT 5124 acceptable to proceed with the study
IND 62,862	1/11/05	Minutes-FDA (Email): Meeting minutes of teleconference on 14 Dec 04
IND 62,862	1/21/05	Submission of protocol amendment to CVT 5123; submission of investigator information in CVT 5131, CVT 5132, and transfer of obligation to CRO for Study CVT 5132
IND 62,862	2/17/05	Submission of investigator information in CVT 5131, CVT 5132, and transfer of obligation to CRO for Study 5131
IND 62,862	3/16/05	Submission of investigator information in CVT 5123, CVT 5124, CVT 5131, CVT 5132, and transfer of obligation to CRO's for CVT 5123 and 5124
IND 62,862	4/15/05	Submission of investigator information in CVT 5131, CVT 5132, and transfer of obligation to CRO for CVT 5131
IND 62,862	5/11/05	Submission of investigator information in CVT 5131 and CVT 5132
IND 62,862	6/8/05	Submission of investigator information in CVT 5131, CVT 5132, and transfer of obligation to CRO for Study CVT 5131
IND 62,862	7/13/05	Submission of investigator information in CVT 5124, CVT 5131 and CVT 5132
IND 62,862	7/24/05	Fax of proposed change to Protocol CVT 5131
IND 62,862	7/24/05	Email follow-up to fax sent 24 Jul 05, copy of fax attached, and Study CVT 5131 protocol Amendment IV attached
IND 62,862	8/4/05	Email response to fax on 24 Jul 05
IND 62,862	8/11/05	Submission of protocol amendment to CVT 5131; submission of investigator information in CVT 5131 and CVT 5132
IND 62,862	8/22/05	Submission of protocol amendment to CVT 5131
IND 62,862	8/22-23/05	Email regarding copy of request for feedback, and status of request for feedback
IND 62,862	8/23/05	Phone regarding clarification on Protocol Amendment for CVT 5131
IND 62,862	8/24/05	Email of Dr. Hung's comments regarding the proposed protocol amendment for CVT 5131
IND 62,862	8/25/05	Fax response to request for information regarding the proposed protocol amendment for CVT 5131
IND 62,862	8/25/05	Email copy of the faxed response to request for information regarding the proposed protocol amendment for CVT 5131
IND 62,862	8/29, 9/1/05	Email status of review of proposed protocol CVT 5131 change
IND 62,862	9/7/05	Email response to fax on 25 Aug 05 regarding the protocol amendment changes for CVT 5131
IND 62,862	10/12/05	Submission of 4th Annual Progress Report
IND 62,862	11/10/05	Submission of investigator information in CVT 5131; submission of technical reports CVT3146.017-R, CVT3146.024-R,a and CVT3146.025-R
IND 62,862	12/14/05	Submission of investigator information in CVT 5131
IND 62,862	12/21/05	Submission of protocol amendment to CVT 5131
IND 62,862	1/23/06	Submission of protocol amendment to CVT 5125
IND 62,862	2/23/06	Submission of investigator information in CVT 5125 and CVT 5131; submission of technical reports CVT3146.117-P, CVT3146.118-P, CVT3146.122-P, CVT3146.125-P, CVT3146.001-N, CVT3146.008-MET, CVT3146.009-MET, CVT3146.010-MET, CVT3146.016-R, CVT3146.026-R, CVT3146.046-N, CVTTOX#04-005, CVT3146.028-T, and transfer of obligation to CRO for Study CVT 5125
IND 62,862	4/4/06	Submission requesting feedback regarding commercial acceptance criteria for drug substance impurities CVT-3145 and N6-methyl CVT-3146

Submission No.	Date	Content
IND 62,862	4/6/06	Email notification of submission 0075 sent 04 Apr 06 regarding a request for feedback
IND 62,862	4/14/06	Submission of protocol amendment for CVT 5126; submission of investigator information in CVT 5126 and CVT 5131
IND 62,862	4/25/06	Phone requesting status of feedback on Pharm/Tox question and identity of new Pharm/Tox reviewer
IND 62,862	5/1/06	Phone explanation of CVT 5132 Data Correction Plan
IND 62,862	5/5, 5/8/06	Email requesting status on the request for feedback (04 Apr 06) from the Pharm/Tox reviewer, and response to request for status on request for feedback (04 Apr 06) from the Pharm/Tox reviewer
IND 62,862	5/9/06	Email request for definition of area % in tables submitted in the request for feedback (04 Apr 06), definition of area % provided in response to the request
IND 62,862	5/19/06	Email response to request for feedback from Pharm/Tox reviewer (04 Apr 06)
IND 62,862	6/9/06	Submission of protocol amendment for CVT 5125; submission of investigator information for CVT 5125. CVT 5126, and CVT 5131
IND 62,862	6/14/06	Submission of Pre-NDA teleconference request – Chemistry and Pharmacology
IND 62,862	6/14/06	Email cover letter and Form FDA 1571 for Serial No. 078
IND 62,862	6/16/06	Submission response to FDA comments in 18 May 06 email, and request for teleconference
IND 62,862	6/18-20/06	Email of cover letter and Form FDA 1571 for Serial No. 0079, scheduling and confirmation of Pre-NDA teleconference
IND 62,862	6/23/06	Submission outline of errors in Study CVT 5132 and plan for correcting the data, and request for feedback
IND 62,862	6/25/06	Email of cover letter and Form FDA 1571 for Serial No. 0080
IND 62,862	6/28/06	Phone regarding question on impurity feedback, confirmation of receipt of email, and timing estimate for NDA and other meetings
IND 62,862	6/29/06	Submission of Pre-NDA CMC-Pharm/Tox Information Package
IND 62,862	6/30/06	Email of E-copy of Serial No. 0081 (Information Package), and confirmation of receipt
IND 62,862	7/3/06	Email question regarding impurities
IND 62,862	7/6/06	Phone regarding transfer of regadenoson project within CDER from DCRP to Division of Medical Imaging and Hematology Products
IND 62,862	7/11/06	Phone follow-up on change in Division responsibility for regadenoson
IND 62,862	7/11-12/06	Phone regarding transfer of IND to Division of Medical Imaging and Hematology Products
IND 62,862	7/12/06	Phone regarding transfer of IND to Division of Medical Imaging and Hematology Products
IND 62,862	7/13/06	Voicemail regarding transfer of IND to Division of Medical Imaging and Hematology Products
IND 62,862	7/14/08	Letter regarding pending transfer of file from DCRP to DMIHP
IND 62,862	7/14/06	Phone follow-up on CVT contacts with the Agency regarding transfer of the IND
IND 62,862	7/14, 7/21/06	Email E-copy of letter regarding pending transfer of file from DCRP to DMIHP, and acknowledgement by Jenkins of CVT discussions with OND staff regarding pending transfer
IND 62,862	7/17/06	Phone follow-up on change in Division responsibility for regadenoson
IND 62,862	7/19-20/06	Phone regarding transfer of IND to DMIHP
IND 62,862	7/20/06	Phone regarding transfer of IND to DMIHP
IND 62,862	7/20/06	Phone regarding pending transfer of file from DCRP to DMIHP

Submission No.	Date	Content
IND 62,862	7/21/06	Email contact information for the week
IND 62,862	7/26-27/06	Email of DCRP meeting minutes from 25 Jul 06 preliminary pre-NDA meeting
IND 62,862	7/27/06	Letter pending transfer of file from DCRP to DMIHP
IND 62,862	7/27-28/06	Email E-copy of the letter responding to communications regarding the pending transfer of file from DCRP to DMIHP, acknowledgement of response from DMIHP
IND 62,862	7/27/06	Phone follow-up on pre-NDA CMC meeting regarding the question on the Division response to question 6 in the Information Package
IND 62,862	8/3/06	Submission of protocol amendment to CVT 5125
IND 62,862	8/9/06	Email feedback on impurity question
IND 62,862	8/29/06	Email of final response to the 0079 submission re: impurities N6-Methyl CVT-3146 and CVT-3145
IND 62,862	9/25-26/06	Email of confirmation of Division transfer, contact in DMIHP
IND 62,862	9/28/06	Email of confirmation of address for IND submission
IND 62,862	9/29/06	Submission of 5th Annual Progress Report: 01 Jun 05 – 31 May 06
IND 62,862	10/27/06	Submission of protocol amendment to CVT 5126; submission of investigator information to CVT 5126; submission of technical report CVT3146.050-N, and technical summaries for CVT3146.050-N, CVT3146.112-P, CVT3146.124-P, CVT3146.128-P, CVT3146.129-P, CVT3146.130-P, and CVT3146.132-P
IND 62,862	11/2/06	Phone regarding Regadenoson regulatory project manager
IND 62,862	11/10/06	Email E-copy of submission 0085: Request for Pre-NDA Meeting (Type B): Clinical
IND 62,862	11/10/06	Submission of request for Pre-NDA Meeting (Type B): Clinical
IND 62,862	11/14; 11/20/06	Phone of Pre-NDA meeting request - Clinical
IND 62,862	11/20/06	Email of scheduling of the Pre-NDA meeting – Clinical
IND 62,862	11/27/06	Letter of request for resubmission of Pre-NDA meeting request and a brief description of Phase 3 primary endpoints
IND 62,862	11/29, 12/4-5/06	Phone regarding scheduling Clinical pre-NDA meeting
IND 62,862	12/4/06	Submission of Pre-NDA meeting request (Type B): Clinical
IND 62,862	12/4/06	Fax of copy of Pre-NDA meeting request (Type B): Clinical
IND 62,862	12/11/06	Phone regarding scheduling of the Pre-NDA meeting
IND 62,862	12/12/06	Phone regarding Regadenoson pre-NDA meeting
IND 62,862	12/15/06	Phone regarding dates for End of Phase 3 and Pre-NDA meetings
IND 62,862	12/18/06	Letter and fax regarding IND 62,862 (Regadenoson)/EOP3 and Pre-NDA meeting granted letter
IND 62,862	12/18-20/06	Phone regarding details on End of Phase 3 and Pre-NDA meetings
IND 62,862	1/3/07	Submission of Information Package: End of Phase 3 and Pre-NDA teleconference
IND 62,862	1/23/07	Fax of Pharmacology/Toxicology information request for End of Phase 3 meeting
IND 62,862	1/22-24/06	Phone regarding End of Phase 3, Pre-NDA and Post-Submission meetings and questions on trade name clearance
IND 62,862	1/25/07	Email regarding draft slides for End of Phase 3 meeting and name of additional meeting participant
IND 62,862	1/26/07	Email of request for Pharmacology/Toxicology information
IND 62,862	1/29/07	Email of FDA participants for End of Phase 3 meeting
IND 62,862	1/29/07	Phone regarding FDA participants for End of Phase 3 meeting, comments from the FDA pre-NDA Meeting and questions on trade name clearance
IND 62,862	1/30/07	Email regarding End of Phase 3 meeting Division comments and information requests

Submission No.	Date	Content
IND 62,862	2/3/07	Email regarding copy of slides from End of Phase 3 meeting
IND 62,862	2/5/07	Email regarding FDA/DMIHP comments for Pre-NDA meeting 06 Feb 07 and CVT teleconference participants
IND 62,862	2/9/07	Email regarding Pre-NDA meeting
IND 62,862	2/15/07	Phone requesting NDA number
IND 62,862	2/15/07	Phone regarding General User Fee information
IND 62,862	2/20/07	Phone regarding minutes for EOP3 and Pre-NDA meetings
IND 62,862	2/20-21/07	Email of EOP3 meeting questions
IND 62,862	2/28/07	Phone follow-up on status of EOP3 and Pre-NDA meeting minutes
IND 62,862	2/28/07	Letter Pre-NDA meeting minutes
IND 62,862	3/2/07	Email regarding Efficacy Dataset Specification for Regadenoson NDA
IND 62,862	3/8/07	Letter End of Phase 3 meeting minutes to sponsor
IND 62,862	3/29-30/07	Phone follow-up on test submission and feedback from Dr. Mucci on dataset specifications
IND 62,862	4/3/07	Email regarding Efficacy dataset for NDA to be sent in EXCEL (or equivalent MINITAB) formatted sets in addition to the SAS formatted sets
IND 62,862	4/4-5/07	Email sample eCTD submission (900162) processed without any issues
IND 62,862	4/24/07	Submission request for feedback on Proposed Trade Name LEXISCAN™
IND 62,862	4/24/07	Letter of three desk copies of submission #0088
IND 62,862	9/28/07	Submission of 6th Annual Progress Report: 01 Jun 06 – 31 May 07
IND 62,862	11/8/07	Email regarding Trade name Pre-Clearance
IND 62,862	1/22/08	Submission of technical report CVT3146.149-P, CVT3146.057-T, and CVT3146.056-T
IND 62,862	1/24/08	Letter of Authorization
NDA 22-161	5/4/06	Phone regarding submission of CDISC Study Data Tabulation Model in eCTD format
NDA 22-161	5/4/06	Email STDM (CDISC) Sample Submission
NDA 22-161	7/26/06	Submission of CTD 900130: Sample Study Data Tabulation Model (SDTM)
NDA 22-161	8/23, 8/25, 8/28/06	Email regarding status of sample submission (CTD 900130) review and request for MedDRA dictionary version
NDA 22-161	8/28-29/06	Email regarding status of sample submission (CTD 900130) review
NDA 22-161	9/8, 9/11/06	Email regarding status of sample submission (CTD 900130) review
NDA 22-161	9/12/06	Email regarding feedback regarding sample submission (CTD 900130)
NDA 22-161	9/26/06	Phone questions regarding FDA comments (CTD 900130)
NDA 22-161	9/26/06	Email questions regarding FDA comments (CTD 900130)
NDA 22-161	9/28/06	Phone regarding FDA response to CVT questions regarding sample SDTM submission (CTD 900130)
NDA 22-161	10/13/06	Email regarding FDA response to remaining questions regarding sample SDTM submission (CTD 900130)
NDA 22-161	12/15, 12/18/06	Email request for sample eCTD number
NDA 22-161	2/15/07	Phone regarding copy of 15 Feb 07 Phone-1 from IND 62,862: Request NDA Number
NDA 22-161	2/15/07	Phone regarding copy of 15 Feb 07 Phone-2 from IND 62,862: General User Fee Information
NDA 22-161	3/2/07	Email regarding efficacy dataset specification for FDA Biostatistician for Regadenoson NDA
NDA 22-161	3/5/07	Submission 900162: Sample eCTD Submission
NDA 22-161	3/20-4/2/07	Email of SDTM test submission 900162 and request for feedback on conformity of the submission
NDA 22-161	3/21, 3/23/07	Phone request for SDTM test submission 900162 email to be resent
NDA 22-161	3/21, 4/4/07	Phone regarding sample eCTD submission follow-up recommendation

Submission No.	Date	Content
NDA 22-161	3/29-30/07	Phone regarding follow-up on test submission and feedback from Dr. Mucci on dataset specifications
NDA 22-161	4/3/07	Email regarding follow-up on acceptability of efficacy dataset specification for NDA (as described in email sent on 02 March 2007): EXCEL (or equivalent MINITAB) formatted sets in addition to the SAS formatted sets
NDA 22-161	4/5/07	Phone regarding status of Sample eCTD submission (900162)
NDA 22-161	4/5/07	Phone regarding Sample eCTD submission (900162) processed without any issues
NDA 22-161	4/4-5/07	Email regarding Sample eCTD submission (900162) processed without any issues
NDA 22-161	5/2/07	Phone requesting priority review and post-submission meeting
NDA 22-161	5/2-3/07	Phone regarding NDA submission acknowledgement, Post-submission meeting and Trade Name Pre-clearance
NDA 22-161	5/14/07	Submission of original NDA
NDA 22-161	5/14/07	Email regarding notification that NDA was submitted by CVT today
NDA 22-161	5/18, 5/21/07	Phone regarding Post-submission meeting date and NDA field copy certification
NDA 22-161	5/21/07	Email confirmation of post-submission meeting date
NDA 22-161	5/22/07	Letter acknowledgement of the receipt of NDA dated 14 May 07
NDA 22-161	6/8, 6/11/07	Phone questions regarding NDA 22-161 and Post-submission meeting
NDA 22-161	6/12/07	Email of CVT Attendees to 19 Jun 07 Post-submission meeting
NDA 22-161	6/15/07	Phone regarding details of Post-submission (Applicant Orientation Presentation) Meeting, and Application had been assigned "Standard" review
NDA 22-161	6/15/07	Email of FDA Attendees for the 19 Jun 07 Applicant Orientation Presentation
NDA 22-161	6/17/07	Email of slides for Application Orientation Presentation
NDA 22-161	6/19/07	Minutes-CVT: Meeting between CVT and FDA regarding Applicant Orientation Presentation Meeting
NDA 22-161	6/21/07	Email regarding Applicant Orientation Presentation Follow-up
NDA 22-161	6/21-22/07	Phone regarding location of Information in NDA
NDA 22-161	6/22/07	Email regarding location of Specific Information in NDA 22-161
NDA 22-161	6/26-28/07	Email regarding Society of Nuclear Medicine presentation slides
NDA 22-161	6/27/07	Email list of study investigators
NDA 22-161	6/27/07	Phone request for location of List of Study Investigators
NDA 22-161	7/13-16/07	Phone regarding possible inspections at sites and Imaging Core Lab
NDA 22-161	7/16/07	Email regarding possible inspections at sites and Imaging Core Lab
NDA 22-161	7/18/07	Email of contact information for possible GCP inspections
NDA 22-161	7/19/07	Email of contact information for possible GCP inspections
NDA 22-161	7/26-30/07	Email of NDA filing letter
NDA 22-161	7/26-31/07	Email regarding CDs for GCP Inspections
NDA 22-161	7/27-30/07	Phone regarding filing letter
NDA 22-161	7/30/07	Fax of NDA filing letter dated 27 Jul 07
NDA 22-161	8/3/07	Letter regarding GCP inspection information sent on CDs by FedEx
NDA 22-161	8/5/07	Email regarding GCP inspection information sent on CDs by FedEx
NDA 22-161	8/7/07	Phone notification of a fax being sent regarding CMC clarification, CMC reviewer's question, and brief discussion on Nonclinical and Clinical questions
NDA 22-161	8/7/07	Fax requesting to provide the correct name, address and CFN number for drug substance manufacturing, in-process testing and release testing site, Hovione LLC

Submission No.	Date	Content
NDA 22-161	8/8, 8/10/07	Email regarding question on how best to provide responses to CMC question
NDA 22-161	8/9/07	Email regarding response to request for drug substance manufacturing site address
NDA 22-161	8/15/07	Phone regarding information from NDA Review Team meeting, brief discussion on CVT's plan for the 4-Month Safety Update, and labeling comments
NDA 22-161	8/17/07	Email regarding response to 27 Jul 07 potential review issues and Nonclinical deficiencies
NDA 22-161	8/22-23/07	Phone regarding inspection at drug substance manufacturer
NDA 22-161	8/27-28/07	Email regarding inquiries from statistician
NDA 22-161	8/30/07	Phone regarding GCP inspections
NDA 22-161	8/30-31/07	Email regarding DIA meeting
NDA 22-161	9/11-14/07	Phone regarding update on Pharm/Tox response and teleconference, questions from statistician, and status of CMC review comments
NDA 22-161	9/11/07	Email of FDA statistician's questions
NDA 22-161	9/14/07	Submission of Safety Update Report and Revised Draft Labeling, and response to 27 Jul 07 filing letter
NDA 22-161	9/15/07	Email regarding confirmation and Dial-in Information for 20 Sep 07 teleconference
NDA 22-161	9/18/07	Email regarding CVT response to FDA statistician's questions
NDA 22-161	9/18/70	Email regarding additional question from FDA statistician
NDA 22-161	9/20/07	Email regarding CVT response to additional FDA statistician's question
NDA 22-161	9/20/07	Minutes-CVT: Potential preclinical review issues from 27 Jul 07 Regadenoson NDA filing
NDA 22-161	9/21-27/07	Phone regarding question on Four-month Safety Update
NDA 22-161	9/24/07	Phone regarding scheduling inspection at core lab
NDA 22-161	9/25-26/07	Email regarding confirmation of GCP inspection dates
NDA 22-161	9/26/07	Email regarding request for feedback on Nonclinical study protocols
NDA 22-161	9/27/07	Email confirming GCP inspections dates
NDA 22-161	10/2/07	Email of letter of confirmation for GCP site inspection
NDA 22-161	10/3/07	Fax regarding Non-clincial study protocols/NDA 22-161 (LEXISCAN™ Regadenoson Injection) and FDA t-con dated 20 Sep 07; and Sponsor response, dated 26 Sep 07
NDA 22-161	10/3-5/07	Phone regarding FDA feedback on Nonclinical protocols, fax of Clinical reviewer comments, and status of CMC reviewer comments
NDA 22-161	10/4/07	Phone regarding dates for additional GCP inspections
NDA 22-161	10/4/07	Email regarding FDA inspections of NDA 22-161
NDA 22-161	10/4-5/07	Phone regarding revised dated for GCP inspections
NDA 22-161	10/5/07	Fax of Clinical comments to Sponsor regarding review of pending NDA
NDA 22-161	10/8/07	Email requesting for clarification of Clinical comments
NDA 22-161	10/9/07	Phone regarding confirmation of inspection dates
NDA 22-161	10/12/07	Phone regarding site inspection
NDA 22-161	10/16/07	Email of CMC IR comments for NDA 22-161 (Regadenoson)
NDA 22-161	10/16/07	Email of information for site inspection
NDA 22-161	10/16/07	Email for plans for travel to inspection sites
NDA 22-161	10/16/07	Email of confirmation letter
NDA 22-161	10/16-17/07	Phone regarding questions on submission of CMC responses, Clinical responses, and Toxicology studies, and no plans for Advisory Committee
NDA 22-161	10/17/07	Email of response to 05 Oct 07 request for additional Clinical information
NDA 22-161	10/17/07	Email of contact information for inspection
NDA 22-161	10/17/07	Phone regarding questions on CMC request for information

Submission No.	Date	Content
NDA 22-161	10/19/07	Submission response to 16 Oct 07 CMC IR comments
NDA 22-161	10/19/07	Email regarding response to 16 Oct 07 CMC IR comments
NDA 22-161	10/19/07	Email regarding travel arrangements
NDA 22-161	10/24-26/07	Phone regarding miscellaneous topics
NDA 22-161	10/25/07	Email regarding changes to Nonclinical protocols and timeline for submission of study reports
NDA 22-161	10/25/07	Email regarding clinical information requested
NDA 22-161	10/26/07	Email of follow-up to clinical questions
NDA 22-161	10/31/07	Email of CVT inspection support team
NDA 22-161	11/1/07	Phone regarding documentation of Quintiles role at Core Lab, question on Low LVEF patients, scheduling demonstration
NDA 22-161	11/1-2/07	Phone regarding submission of stability data, and scheduling "Image Reading" Demonstration
NDA 22-161	11/5/07	Email of CVT contact information
NDA 22-161	11/7/07	Email regarding availability for Image Reading Demonstration, and response to requests for Clinical information
NDA 22-161	11/14/07	Email of Clinical question
NDA 22-161	11/16/07	Letter and Email of CMC information request due by 23 Nov 07
NDA 22-161	11/16/07	Phone regarding timing for response to CMC information request
NDA 22-161	11/26/07	Submission response to 16 Nov 07 CMC information request letter
NDA 22-161	11/26/07	Email of Clinical question
NDA 22-161	11/26-27/07	Email regarding response to 16 Nov 07 CMC IR letter
NDA 22-161	11/29/07	Phone follow-up on submission of CMC and Clinical responses
NDA 22-161	11/30/07	Submission of follow-up response to 16 Oct 07 CMC IR comments and Revised Draft Carton Label for syringe
NDA 22-161	11/30/07	Email of CMC Stability update
NDA 22-161	11/30/07	Submission 26 Nov 07 response to 14 Nov 07 request for Clinical information
NDA 22-161	12/3/07	Submission responses and correspondences related to Nonclinical studies
NDA 22-161	12/3/07	Submission of CVT 5132 clinical study report – correction to AE and SAE listings
NDA 22-161	12/3/07	Email of GCP inspection information
NDA 22-161	12/5/07	Phone regarding update on recent submissions, expecting timing of feedback from DMETS on Tradename, and plans for Image Demonstration at FDA
NDA 22-161	12/12/07	Submission of new Nonclinical study reports CVT3146.149-P, and CVT3146.057-T
NDA 22-161	12/12/07	Letter and Email of CMC Information Request
NDA 22-161	12/14/07	Email of Image Reading Demonstration – 17 Dec 07 List of CVT participants
NDA 22-161	12/17/07	Minutes-CVT: Meeting between CVT and FDA regarding Image Reading Demonstration Meeting Minutes
NDA 22-161	12/18/07	Phone regarding plans for vacations, follow-up after FDA meeting, timing of CMC response, submission of Nonclinical report, and labeling review
NDA 22-161	12/18/07	Submission response to 12 Dec 07 CMC IR letter
NDA 22-161	12/19/07	Email response to 12 Dec 07 CMC IR
NDA 22-161	12/21/07	Submission of new Nonclinical study report of CVT3146.056-T
NDA 22-161	12/21/07	Email regarding submission of final Nonclinical study report
NDA 22-161	12/21/07	Email regarding location of reader segment scores in NDA CRT Datasets
NDA 22-161	1/4/08	Phone regarding information needed for Microbiology Review
NDA 22-161	1/7/08	Submission response to 04 Jan 08 Microbiology Request
NDA 22-161	1/7/08	Email of response to 04 Jan 08 Microbiology Request

Submission No.	Date	Content
NDA 22-161	1/8-11/08	Phone regarding status of feedback on Trade name and NDA Review
NDA 22-161	1/17-18/08	Phone regarding status of Trade name Review and Pharm/Tox Information Request
NDA 22-161	1/22-23/08	Phone regarding status of NDA Review and Trade name Clearance
NDA 22-161	1/22-24/08	Email of question from Pharm/Tox reviewer
NDA 22-161	1/28-29/08	Phone regarding notification of inspection at CVT for CVT 5131 and CVT 5132
NDA 22-161	1/29-30/08	Phone regarding timing/plan for FDA's Labeling comments, and question regarding inspection at CVT
NDA 22-161	1/29-30/08	Phone questions regarding CVT inspection
NDA 22-161	1/31/08	Form FDA 482: FDA inspection of CVT; Announced inspection for Regadenoson (Form FDA 483 inspectional observations was not issued)
NDA 22-161	2/5/08	Phone regarding single dose bridging study results and teleconference with FDA
NDA 22-161	2/7/08	Email of summary document and CVT participants for the teleconference 0 07 Feb 08
NDA 22-161	2/7/08	Minutes-CVT: FDA comments on Nonclinical bridging study results
NDA 22-161	2/11/08	Phone follow-up on Pharm/Tox
NDA 22-161	2/12/08	Phone regarding additional Pharm/Tox discussion
NDA 22-161	2/18/08	Submission of Assessment of clinical relevance of histopathology finding in single dose toxicity study in rats (CVT3146.056-T)
NDA 22-161	2/19/08	Email regarding assessment of histopathology finding from single dose toxicity study (CVT3146.056-T)
NDA 22-161	2/19-20/08	Phone follow-up on Pharm/Tox submission
NDA 22-161	2/20/08	Phone regarding NDA review status
NDA 22-161	2/20/08	Email follow-up on GCP inspection held at CVT for CVT 5131 and CVT 5132
NDA 22-161	2/20/08	Phone regarding response to information request for Nuclear Core Laboratory
NDA 22-161	2/22/08	Letter response to Information Request for Nuclear Core Laboratory
NDA 22-161	2/22/08	Email response to Information Request for Nuclear Core Laboratory (1 of 4)
NDA 22-161	2/22/08	Email response to Information Request for Nuclear Core Laboratory (2 of 4)
NDA 22-161	2/22/08	Email response to Information Request for Nuclear Core Laboratory (3 of 4)
NDA 22-161	2/22/08	Email response to Information Request for Nuclear Core Laboratory (4 of 4)
NDA 22-161	2/25, 2/27/08	Phone regarding follow-up on NDA review
NDA 22-161	2/26/08	Email of CMC and Clinical question
NDA 22-161	2/27/08	Email response to CMC and Clincal question
NDA 22-161	2/27/08	Submission response to 26 Feb 08 Clinical and Chemistry comments
NDA 22-161	2/28/08	Phone regarding outcome of Pharm/Tox assessment and status of NDA review
NDA 22-161	2/28/08	Phone follow-up after teleconference
NDA 22-161	2/28/08	Submission of copy of Summary Document for 07 Feb 08 Pharm/Tox teleconference
NDA 22-161	2/29/08	Phone follow-up on submission of Core Lab documentation
NDA 22-161	3/4/08	Email of Information Request on reading session and reading room
NDA 22-161	3/6/08	Email of response to Information Request on reading session and reading room
NDA 22-161	3/7/08	Email of FDA Draft Label for Regadenoson Injection

Submission No.	Date	Content
NDA 22-161	3/8/08	Email response to question on Access Database
NDA 22-161	3/10/08	Email regarding additional comments on package insert and carton/container labels
NDA 22-161	3/10/08	Email of Regadenoson Labeling
NDA 22-161	3/10-11/08	Phone regarding submission of response to FDA's Draft Labeling
NDA 22-161	3/10-11/08	Phone regarding NDA review status
NDA 22-161	3/11/08	Email regarding adverse reactions email address contact information
NDA 22-161	3/11/08	Email regarding vial/carton package drawings/labeling
NDA 22-161	3/11/08	Email regarding vial/carton package drawings/labeling - REVISED
NDA 22-161	3/11/08	Email regarding comments from CMC and FDA labeling team on CVT package drawings and package insert
NDA 22-161	3/12/08	Email regarding vial/carton package drawings/labeling, additional recommendations on labeling, and question regarding presentation of trade name
NDA 22-161	3/12/08	Phone regarding Trade name and Labeling status
NDA 22-161	3/13/08	Email of Clinical information request
NDA 22-161	3/13/08	Phone regarding label and review status
NDA 22-161	3/13/08	Phone regarding label review
NDA 22-161	3/13/08	Email regarding response to Clinical Information Request
NDA 22-161	3/18/08	Phone regarding labeling status
NDA 22-161	3/20/08	Phone regarding labeling status
NDA 22-161	3/21/08	Phone regarding labeling status
NDA 22-161	3/24/08	Phone regarding labeling/NDA status
NDA 22-161	3/24/08	Email regarding labeling, postmarketing commitments and CVT response to labeling comments
NDA 22-161	3/25/08	Phone regarding NDA status
NDA 22-161	3/25/08	Email regarding CVT participants on 25 March teleconference
NDA 22-161	3/25/08	Minutes-CVT: Meeting minutes for teleconference between CVT, Astellas Pharma US and FDA
NDA 22-161	3/25/08	Minutes-Astellas: Minutes for teleconference between CVT, Astellas Pharma US and FDA
NDA 22-161	3/25/08	Email regarding post-marketing commitments
NDA 22-161	3/25/08	Email regarding revised SPL
NDA 22-161	3/26/08	Phone regarding SPL file and comments on package labeling
NDA 22-161	3/26/08	Email regarding packaging information and CVT response
NDA 22-161	3/27/08	Phone regarding follow-up on package labels, SPL and review
NDA 22-161	3/28/08	Phone regarding status update
NDA 22-161	3/28/08	Email regarding Word version of package drawings
NDA 22-161	3/28/08	Fax: resending post-marketing commitments (25 Mar 2008)
NDA 22-161	4/1-2/08	Phone regarding NDA status
NDA 22-161	4/3/08	Phone regarding NDA status
NDA 22-161	4/4/08	Phone regarding NDA status
NDA 22-161	4/7/08	Phone regarding NDA status
NDA 22-161	4/7/08	Phone regarding NDA status
NDA 22-161	4/8/08	Phone regarding NDA status
NDA 22-161	4/8/08	Email regarding NDA status
NDA 22-161	4/8-9/08	Email regarding NDA status
NDA 22-161	4/9/08	Phone regarding NDA status
NDA 22-161	4/9/08	Email regarding final version of labeling for review
NDA 22-161	4/9/08	Phone regarding NDA status
NDA 22-161	4/9/08	Phone regarding NDA approval

Submission No.	Date	Content
NDA 22-161	4/10/08	Phone regarding NDA status
NDA 22-161	4/10/08	Email: Lexiscan approval letter
NDA 22-161	4/10/08	Phone regarding NDA approval letter
NDA 22-161	4/11/08	Email regarding Lexiscan listing on drugs@fda.com site
NDA 22-161	4/11/08	Phone regarding FDA approval
NDA 22-161	4/11/08	Phone regarding correction of FDA posting of Lexiscan information on drugs@fda.com site

12. Eligibility for extension of patent term

In the opinion of CV Therapeutics, Inc., US Patent No. 6,403,567 is eligible for the requested extension of patent term.

The maximum length of extension available for US Patent No. 6,403,567 based on approval of Lexiscan ™ (regadenoson 0.4 mg/5 mL injectable solution) will be 1024 days (2 years, 9 months, and 20 days), and the length of extension will be determined as follows:

The regulatory review period — 35 USC 156(g)(1)(B)

The regulatory review period started on August 2, 2001, the day that IND 62,862 became effective; this was prior to the issuance of US Patent No. 6,403,567 on June 11, 2002. The regulatory review period ended April 10, 2008. The regulatory review period has therefore lasted 6 years, 8 months, and 9 days 2444 days.

As 53 U.S.C. § 156(c) limits the period of time which may be extended to a time "equal to the regulatory review period for the approved product which period occurs after the date the patent is issued," the portion of the regulatory review period which may be used to calculate the extension is limited to 5 years and 10 months which is 2131 days.

The IND period — 35 USC 156(g)(1)(B)(i)

The period from the issuance of US Patent No. 6,403,567 on June 11, 2002, to the date of submission of NDA 22-161 on May 14, 2007, is 4 years, 11 months, 4 days (1798 days); one-half this period is 899 days.

The NDA period — 35 USC 156(g)(1)(B)(ii)

The period from the date of submission of NDA 22-161 on May 14, 2007, to the date of approval of the NDA on April 10, 2008, is 0 years, 10 months, and 28 days (333 days).

Calculation of maximum extension on approval — 35 USC 156(c)

The maximum permissible extension is calculated as the sum of one-half the IND period (899 days) and the whole NDA period (333 days), for a total of at least 1232 days (3 years, 4 months, and 14 days). When added to the remaining patent term of U.S. Patent No. 6,403,567, the resulting total term of the patent remaining after the approval of the approved product including the extension is 14 years, 6 months, and 26 days, which exceeds the maximum 14-year term pursuant to 35 USC 156(c)(3). Accordingly, CV Therapeutics, Inc., expects that the length of extension available for US Patent No. 6,403,567 based on approval of Lexiscan ™ (regadenoson 0.4 mg/5 mL injectable solution), will be 1024 days (2 years, 9 months, and 20 days), which will expire on April 10, 2022, when granted.

13. Duty of Disclosure

CV Therapeutics, Inc., acknowledges a duty to disclose to the Director of the US Patent & Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought herein.

In an effort to comply with the aforementioned duty, CV Therapeutics, Inc., wishes to make the Director aware that an Application for Extension of Patent Term for US Patent 6,642,210 has been contemporaneously submitted to the US Patent & Trademark Office on the same day of filing of the present Application.

CV Therapeutics, Inc. also wishes to make the Director aware that CV Therapeutics Inc. was the NDA applicant throughout the regulatory review period and that the NDA was transferred to Astellas Pharma US, Inc. on April 17, 2008.

14. Fees

The Commissioner is hereby authorized to charge $1,120.00 (37 CFR 1.20(j)(1)) and any underpayment or credit any overpayment to Deposit Account No. 50-1789, referencing matter 99-0423.

15. Name and address for correspondence

Inquiries and correspondence relating to this Application for extension of patent term should be directed to:

Customer Number 27716.

Telephone inquiries should be directed to:

Daniel W. Collins at 650-384-8047
VP, Legal - Intellectual Property
CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304

Faxed correspondence should be directed to:
Daniel W. Collins, 650-475-0359

16. Multiple copies

This Application for extension of patent term is being submitted in an original and two copies. The undersigned hereby certifies that the copies of this Application filed herewith are true and correct copies.

17. Declaration

The undersigned duly authorized agent for CV Therapeutics, Inc., hereby declares that:

(1) he is a patent attorney authorized to practice before the US Patent & Trademark Office and is authorized to represent CV Therapeutics, Inc., in this Application for extension of patent term by virtue of a Power of Attorney executed on June 3, 2008. A copy of the Power of Attorney is attached hereto as Attachment D;

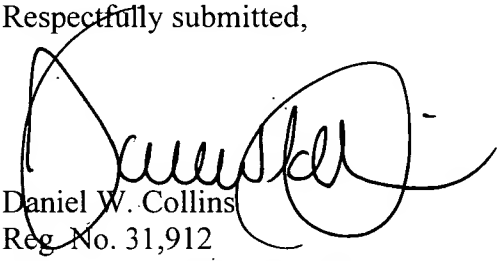
(2) he has reviewed and understands the contents of this Application;

(3) he believes that US Patent No. 6,403,567 is subject to extension pursuant to 35 USC 156(d)(1) and 37 CFR 1.710;

(4) he believes that an extension of the length claimed is justified under 35 USC 156 and the applicable regulations; and

(5) he believes that US Patent No. 6,403,567 meets the conditions for extension of the term of a patent set forth in 37 CFR 1.720.

Respectfully submitted,



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VP, Legal - Intellectual Property
CV Therapeutics, Inc.

June 6, 2008

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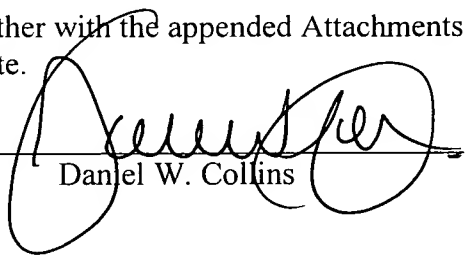
Facsimile: 650-475-0359
daniel.collins@cvt.com

This is to certify that the copy of this Application (together with the appended Attachments "A" through "D" filed herewith is a true and correct duplicate.

Date: June 6, 2008



Daniel W. Collins

ATTACHMENT A
COPY OF US PATENT NO. 6,403,567

US006403567B1

(12) **United States Patent**
Zablocki et al.

(10) **Patent No.: US 6,403,567 B1**
(45) **Date of Patent: Jun. 11, 2002**

(54) **N-PYRAZOLE A2A ADENOSINE RECEPTOR AGONISTS**

(75) Inventors: **Jeff A. Zablocki**, Mountain View; **Elfatih O. Elzein**, Freemont; **Venkata P. Palle**, Mountain View, all of CA (US)

(73) Assignee: **CV Therapeutics, Inc.**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/338,185**

(22) Filed: **Jun. 22, 1999**

(51) **Int. Cl.**[7] **A61K 31/70**; C07H 19/167

(52) **U.S. Cl.** **514/46**; 536/27.3; 536/27.6; 536/27.61; 536/27.62; 536/27.63

(58) **Field of Search** 514/46; 536/27.3, 536/27.6, 27.61, 27.62, 27.63

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,956,345	A	9/1990	Miyasaka et al.	514/46
4,968,697	A	* 11/1990	Hutchison	514/46
5,189,027	A	2/1993	Miyashita et al.	514/46
5,270,304	A	12/1993	Kogi et al.	514/46
5,459,254	A	10/1995	Yamaguchi et al.	536/27.11
5,593,975	A	1/1997	Cristalli	514/46
5,705,491	A	1/1998	Yamada	514/46
5,770,716	A	6/1998	Khan et al.	536/23.1
5,939,543	A	8/1999	Morozumi et al.	536/27.63

FOREIGN PATENT DOCUMENTS

CA	965411	4/1975
EP	354 638	2/1990
JP	Hei 5[1993]-9197	1/1993

OTHER PUBLICATIONS

Marumoto, et al., "Synthesis and Coronary Vadodilating Activity of 2–Substituted Adenosines", *Chem.. Pharm. Bull.* 23(4): 759–774 (1975).

Marumoto, et al., "Synthesis and Enzymatic Activity of Adenosine 3',5'–Cyclic Phosphate Analogs", *Chem.. Pharm. Bull.* 27(4) 990–1003 (1979).

Persson, et al., "Synthesis and Antiviral Effects of 2–Heteroaryl Substituted Adenosine and 8–Heteroaryl Substituted Guanosine Derivatives", *Bioorganic & Medicinal Chemistry*, 3:1377–1382 (1995).

Mager, et al., "Molecular simulation applied to 2–(N'alkylidenehydrazino)–and 2–(N'–aralkylidenehydrazino) adenosine A_2 Agnonists", *Eur J. Med. Chem*, 30:15–25 (1995).

Cristalli et al., "2–Alkynl Derivatives of Adenosine 5'–N'ethyluronamide: Selective A_2 Adenosine Receptor Agonists with Potent Inhibitory Activity on Platelet Aggregation", *J. Med. Chem*, 37:1720–1726 (1994). (May 27, 1994).

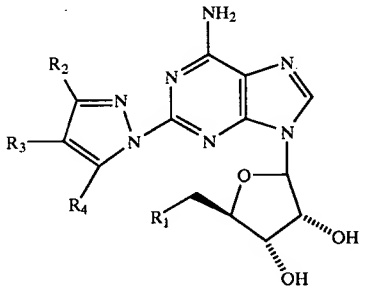
Matsuda, et al., "Nucleosides and Nucleotides. 103. 2 – Alkynyladenoines: A Novel Class of Selective Adenosine A_2 Receptor Agonists with Potent Antihypertensive Effects", *J. Med. Chem.* 35:241–252 (1992). (Jan. 24, 1992).

* cited by examiner

Primary Examiner—Paul J. Killos
Assistant Examiner—L. Eric Crane
(74) *Attorney, Agent, or Firm*—McDonnell Boehnen Hulbert & Berghoff

(57) **ABSTRACT**

2-adenosine N-pyrazole compositions having the following formula:



and methods for using the compositions as A2A receptor agonists to stimulate mammalian coronary vasodilatation for therapeutic purposes and for purposes of imaging the heart.

13 Claims, No Drawings

N-PYRAZOLE A2A ADENOSINE RECEPTOR AGONISTS

BACKGROUND OF THE INVENTION

1. Field of Invention

This invention includes N-pyrazole substituted 2-adenosine compositions that are useful as A_{2A} receptor agonists. The compositions of this invention are vasodialating agents that are useful as heart imaging aids that aid in the identification of mammals, and especially humans who are suffering from coronary disorders such poor coronary perfusion which is indicative of coronary artery disease (CAD). The compositions of this invention can also be used as therapeutics for coronary artery disease as well as any other disorders mediated by the A_{2A} receptor.

2. Description of the Art

Pharmacological stress is frequently induced with adenosine or dipyridamole in patients with suspected CAD before imaging with T1 scintigraphy or echocardiography. Both drugs effect dilation of the coronary resistance vessels by activation of cell surface A_2 receptors. Although pharmacological stress was originally introduced as a mean of provoking coronary dilation in patients unable to exercise, several studies have shown that the prognostic value of ^{201}T1 or echocardiographic imaging in patients subjected to pharmacological stress with adenosine or dipyridamole was equivalent to patients subjected to traditional exercise stress tests. However, there is a high incidence of drug-related adverse side effects during pharmacological stress imaging with these drugs such as headache and nausea, that could be improved with new therapeutic agents.

Adenosine A_{2B} and A3 receptors are involved in a mast cell degranulation and, therefore, asthmatics are not give the non-specific adenosine agonists to induce a pharmacological stress test. Additionally, adenosine stimulation of the A_1 receptor in the atrium and A-V mode will diminish the S-H interval which can induce AV block (N. C. Gupto et al.; *J. Am Coll. Cardiol*; (1992) 19: 248–257). Also, stimulation of the adenosine A_1 receptor by adenosine may be responsible for the nausea since the A_1 receptor is found in the intestinal tract (J. Nicholls et al.; *Eur. J. Pharm.* (1997) 338(2) 143–150).

Animal data suggests that specific adenosine A_{2A} subtype receptors on coronary resistance vessels mediate the coronary dilatory responses to adenosine, whereas subtype A_{2B} receptor stimulation relaxes peripheral vessels (note: the latter lowers systemic blood pressure). As a result there is a need for pharmaceutical compositions that are A_{2A} receptor agonists that have no pharmacological effect as a result of stimulating the A_1 receptor in vivo. Furthermore, there is a need for A_{2A} receptor agonists that have a short half-life, and that are well tolerated by patients undergoing pharmacological coronary stress evaluations.

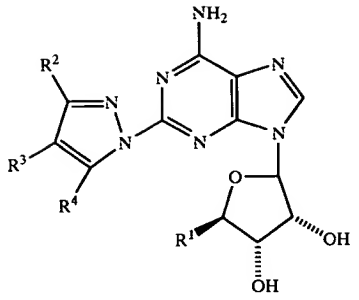
SUMMARY OF THE INVENTION

In one aspect, this invention includes 2-adenosine N-pyrazole compositions that are useful A_{2A} receptor agonists.

In another aspect, this invention includes pharmaceutical compositions including 2-adenosine N-pyrazole that are well tolerated with few side effects.

Still another aspect of this invention are N-pyrazole compositions that can be easily used in conjunction with radioactive imaging agents to facilitate coronary imaging.

In one embodiment, this invention includes 2-adenosine N-pyrazole compositions having the following formula:

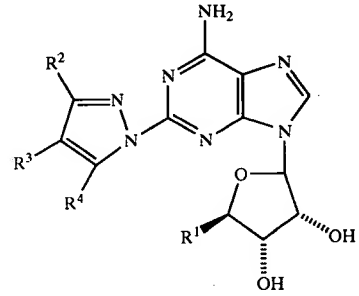


In another embodiment, this invention includes methods for using compositions of this invention to stimulate coronary vasodilatation in mammals, and especially in humans, for stressing the heart induced steal situation for purposes of imaging the heart.

In still another embodiment, this invention is a pharmaceutical composition of matter comprising one or more compositions of this invention and one or more pharmaceutical excipients.

DESCRIPTION OF THE CURRENT EMBODIMENT

This invention includes a new class of 2-adenosine N-pyrazoles having the formula:



wherein R^1=CH_2OH, —$CONR_5R_6$;

R^3 is independently selected from the group consisting of $C_{1\text{-}15}$ alkyl, halo, NO_2, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$,—$CONR^7R^8$, $C_{2\text{-}15}$ alkenyl, $C_{2\text{-}15}$ alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, NO_2, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO^2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$, $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R_{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$ and wherein the optional substituted heteroaryl, aryl, and heterocyclyl substituents are optionally substituted with halo, NO_2, alkyl, CF_3, amino, mono- or di-alkylamino, alkyl or aryl or heteroaryl amide, $NCOR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON$

$(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, or OR^{20};

R^5 and R^6 are each individually selected from H, and C_1–C_{15} alkyl that is optionally substituted with from 1 to 2 substituents independently selected from the group of halo, NO_2, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$, $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$ wherein each optional substituted heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with halo, NO_2, alkyl, CF_3, amino, monoalkylamino, dialkylamino, alkylamide, arylamide, heteroarylamide, $NCOR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, and OR^{20};

R^7 is selected from the group consisting of hydrogen, $C_{1\text{-}15}$ alkyl, $C_{2\text{-}15}$ alkenyl, $C_{2\text{-}15}$ alkynyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group of halo, NO_2, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$, $NR^{20}COR^{22}$, $NR^{20}CO_2R_{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$ and $OCON(R^{20})_2$ and wherein each optional substituted heteroaryl, aryl and heterocyclyl substituent is optionally substituted with halo, NO_2, alkyl, CF_3, amino, mono- or di-alkylamino, alkyl or aryl or heteroaryl amide, $NCOR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, and OR^{20};

R^8 is selected from the group consisting of hydrogen, $C_{1\text{-}15}$ alkyl, $C_{2\text{-}15}$ alkenyl, $C_{2\text{-}15}$ alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, NO_2, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R_{20})_2$, $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R_{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$ and wherein each optional substituted heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with halo, NO_2, alkyl, CF_3, amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, $NCOR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, and OR^{20};

R^{20} is selected from the group consisting of H, $C_{1\text{-}15}$ alkyl, $C_{2\text{-}15}$ alkenyl, $C_{2\text{-}15}$ alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O—$C_{1\text{-}6}$ alkyl, CF_3, aryl, and heteroaryl;

R^{22} is selected from the group consisting of $C_{1\text{-}15}$ alkyl, $C_{2\text{-}15}$ alkenyl, $C_{2\text{-}15}$ alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O—$C_{1\text{-}6}$ alkyl, CF_3, aryl, and heteroaryl; and

wherein R^2 and R^4 are selected from the group consisting of H, $C_{1\text{-}6}$ alkyl and aryl, wherein the alkyl and aryl substituents are optionally substituted with halo, CN, CF_3, OR^{20} and $N(R^{20})_2$ with the proviso that when R^2 is not hydrogen then R^4 is hydrogen, and when R^4 is not hydrogen then R^2 is hydrogen.

In preferred compositions of this invention, R^3 is selected from the group consisting of $C_{1\text{-}15}$ alkyl, halo, CF_3, CN, OR^{20}, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, COR^{20}, CO_2R^{20}, —$CONR^7R^8$, aryl and heteroaryl wherein the alkyl, aryl and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, COR^{20}, CO_2R^{20} or $CON(R^{20})_2$, and each optional heteroaryl and aryl substituent is optionally substituted with halo, alkyl, CF_3 CN, and OR^{20}; R^5 and R^6 are independently selected from the group of H and C_1–C_{15} alkyl including one optional aryl substituent and each optional aryl substituent that is optionally substituted with halo or CF_3; R^7 is selected from the group consisting of $C_{1\text{-}15}$ alkyl, $C_{2\text{-}15}$ alkynyl, aryl, and heteroaryl, wherein the alkyl, alkynyl, aryl, and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, CF_3, CN, OR^{20}, and each optional heteroaryl and aryl substituent is optionally substituted with halo, alkyl, CF_3, CN, or OR^{20}; R^8 is selected from the group consisting of hydrogen and $C_{1\text{-}15}$ alkyl; R^{20} is selected from the group consisting of H, $C_{1\text{-}4}$ alkyl and aryl, wherein alkyl and aryl substituents are optionally substituted with one alkyl substituent; and R^{22} is selected from the group consisting of $C_{1\text{-}4}$ alkyl and aryl which are each optionally substituted with from 1 to 3 alkyl group.

In more preferred compositions, R^1 is CH_2OH; R^3 is selected from the group consisting of CO_2R^{20}, —$CONR^7R^8$ and aryl where the aryl substituent is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, $C_{1\text{-}6}$ alkyl, CF_3 and OR^{20}; R^7 is selected from the group consisting of hydrogen, $C_{1\text{-}8}$ alkyl and aryl, where the alkyl and aryl substituents are optionally substituted with one substituent selected from the group consisting of halo, aryl, CF_3, CN, OR^{20} and wherein each optional aryl substituent is optionally substituted with halo, alkyl, CF_3 CN, and OR^{20}; R^8 is selected from the group consisting of hydrogen and $C_{1\text{-}8}$ alkyl; and R^{20} is selected from hydrogen and $C_{1\text{-}4}$ alkyl.

In a still more preferred embodiment, R^1=CH_2OH; R^3 is selected from the group consisting of CO_2R^{20}, —$CONR^7R^8$, and aryl that is optionally substituted with one substituent selected from the group consisting of halo, $C_{1\text{-}3}$ alkyl and OR^{20}; R^7 is selected from of hydrogen, and $C_{1\text{-}3}$ alkyl; R^8 is hydrogen; and R^{20} is selected from hydrogen and $C_{1\text{-}4}$ alkyl. In this preferred embodiment, R^3 is most preferably selected from —CO_2Et and —CONHEt.

In another still more preferred embodiment, R^1=—CONHEt, R^3 is selected from the group consisting of CO_2R^{20}, —$CONR^7R^8$, and aryl in that aryl is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, $C_{1\text{-}3}$ alkyl, CF_3 or OR^{20}; R^7 is selected from the group consisting of hydrogen, and $C_{1\text{-}8}$ alkyl that is optionally substituted with one substituent selected from the group consisting of halo,

CF_3, CN or OR^{20}; R^8 is selected from the group consisting of hydrogen and C_{1-3} alkyl; and R^{20} is selected from the group consisting of hydrogen and C_{1-4} alkyl. In this more preferred embodiment, R^8 is preferably hydrogen, R^7 is preferably selected from the group consisting of hydrogen, and C_{1-3}, and R^{20} is preferably selected from the group consisting of hydrogen and C_{1-4} alkyl.

In a most preferred embodiment, the composition of this invention is selected from ethyl1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylate, (4S,2R,3R,5R)-2-{6-amino-2-[4-(4-chlorophenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol, (4S,2R,3R,5R)-2-{6-amino-2-[4-(4-methoxyphenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol, (4S,2R,3R,5R)-2-{6-amino-2-[4-(4-methylphenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl) oxolane-3,4-diol, (1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide, 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylic acid, and mixtures thereof.

The following definitions apply to terms as used herein.

"Halo" or "Halogen"—alone or in combination means all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), iodo (I).

"Hydroxyl" refers to the group —OH.

"Thiol" or "mercapto" refers to the group —SH.

"Alkyl"—alone or in combination means an alkane-derived radical containing from 1 to 20, preferably 1 to 15, carbon atoms (unless specifically defined). It is a straight chain alkyl, branched alkyl or cycloalkyl. Preferably, straight or branched alkyl groups containing from 1–15, more preferably 1 to 8, even more preferably 1–6, yet more preferably 1–4 and most preferably 1–2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl and the like. The term "lower alkyl" is used herein to describe the straight chain alkyl groups described immediately above. Preferably, cycloalkyl groups are monocyclic, bicyclic or tricyclic ring systems of 3–8, more preferably 3–6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, adamantyl and the like. Alkyl also includes a straight chain or branched alkyl group that contains or is interrupted by a cycloalkyl portion. The straight chain or branched alkyl group is attached at any available point to produce a stable compound. Examples of this include, but are not limited to; 4-(isopropyl)-cyclohexylethyl or 2-methyl-cyclopropylpentyl. A substituted alkyl is a straight chain alkyl, branched alkyl, or cycloalkyl group defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like.

"Alkenyl"—alone or in combination means a straight, branched, or cyclic hydrocarbon containing 2–20, preferably 2–17, more preferably 2–10, even more preferably 2–8, most preferably 2–4, carbon atoms and at least one, preferably 1–3, more preferably 1–2, most preferably one, carbon to carbon double bond. In the case of a cycloalkyl group, conjugation of more than one carbon to carbon double bond is not such as to confer aromaticity to the ring. Carbon to carbon double bonds may be either contained within a cycloalkyl portion, with the exception of cyclopropyl, or within a straight chain or branched portion. Examples of alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, cyclohexenyl, cyclohexenylalkyl and the like. A substituted alkenyl is the straight chain alkenyl, branched alkenyl or cycloalkenyl group defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, or the like attached at any available point to produce a stable compound.

"Alkynyl"—alone or in combination means a straight or branched hydrocarbon containing 2–20, preferably 2–17, more preferably 2–10, even more preferably 2–8, most preferably 2–4, carbon atoms containing at least one, preferably one, carbon to carbon triple bond. Examples of alkynyl groups include ethynyl, propynyl, butynyl and the like. A substituted alkynyl refers to the straight chain alkynyl or branched alkenyl defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like attached at any available point to produce a stable compound.

"Alkyl alkenyl" refers to a group —R—CR'=CR'"R"", where R is lower alkyl, or substituted lower alkyl, R', R'", R"" may independently be hydrogen, halogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined below.

"Alkyl alkynyl" refers to a groups —RC≡CR' where R is lower alkyl or substituted lower alkyl, R' is hydrogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined below.

"Alkoxy" denotes the group —OR, where R is lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroalkyl, heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, or substituted cycloheteroalkyl as defined.

"Alkylthio" denotes the group —SR, $—S(O)_{n=1-2}—R$, where R is lower alkyl, substituted lower alkyl, aryl, substituted aryl, aralkyl or substituted aralkyl as defined herein.

"Acyl" denotes groups —C(O)R, where R is hydrogen, lower alkyl substituted lower alkyl, aryl, substituted aryl and the like as defined herein.

"Aryloxy" denotes groups —OAr, where Ar is an aryl, substituted aryl, heteroaryl, or substituted heteroaryl group as defined herein.

"Amino" denotes the group NRR', where R and R' may independently by hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined herein or acyl.

"Amido" denotes the group —C(O)NRR', where R and R' may independently by hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, substituted hetaryl as defined herein.

"Carboxyl" denotes the group —C(O)OR, where R is hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, and substituted hetaryl as defined herein.

"Aryl"—alone or in combination means phenyl or naphthyl optionally carbocyclic fused with a cycloalkyl of preferably 5–7, more preferably 5–6, ring members and/or optionally substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like.

"Substituted aryl" refers to aryl optionally substituted with one or more functional groups, e.g., halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heterocycle" refers to a saturated, unsaturated, or aromatic carbocyclic group having a single ring (e.g., morpholino, pyridyl or furyl) or multiple condensed rings (e.g., naphthpyridyl, quinoxalyl, quinolinyl, indolizinyl or benzo[b]thienyl) and having at least one hetero atom, such as N, O or S, within the ring, which can optionally be unsubstituted or substituted with, e.g., halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroaryl"—alone or in combination means a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1–4, more preferably 1–3, even more preferably 1–2, heteroatoms independently selected from the group O, S, and N, and optionally substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable aromatic ring is retained. Examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrazinyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazinyl, furanyl, benzofuryl, indolyl and the like. A substituted heteroaryl contains a substituent attached at an available carbon or nitrogen to produce a stable compound.

"Heterocyclyl"—alone or in combination means a non-aromatic cycloalkyl group having from 5 to 10 atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N, and are optionally benzo fused or fused heteroaryl of 5–6 ring members and/or are optionally substituted as in the case of cycloalkyl. Heterocycyl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. The point of attachment is at a carbon or nitrogen atom. Examples of heterocyclyl groups are tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, piperazinyl, dihydrobenzofuryl, dihydroindolyl, and the like. A substituted hetercyclyl contains a substituent nitrogen attached at an available carbon or nitrogen to produce a stable compound.

"Substituted heteroaryl" refers to a heterocycle optionally mono or poly substituted with one or more functional groups, e.g., halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Aralkyl" refers to the group —R—Ar where Ar is an aryl group and R is lower alkyl or substituted lower alkyl group. Aryl groups can optionally be unsubstituted or substituted with, e.g., halogen, lower alkyl, alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroalkyl" refers to the group —R—Het where Het is a heterocycle group and R is a lower alkyl group. Heteroalkyl groups can optionally be unsubstituted or substituted with e.g., halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroarylalkyl" refers to the group —R—HetAr where HetAr is an heteroaryl group and R lower alkyl or substituted lower alkyl. Heteroarylalkyl groups can optionally be unsubstituted or substituted with, e.g., halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio, acetylene, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Cycloalkyl" refers to a divalent cyclic or polycyclic alkyl group containing 3 to 15 carbon atoms.

"Substituted cycloalkyl" refers to a cycloalkyl group comprising one or more substituents with, e.g., halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio, acetylene, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Cycloheteroalkyl" refers to a cycloalkyl group wherein one or more of the ring carbon atoms is replaced with a heteroatom (e.g., N, O, S or P).

Substituted cycloheteroalkyl" refers to a cycloheteroalkyl group as herein defined which contains one or more substituents, such as halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

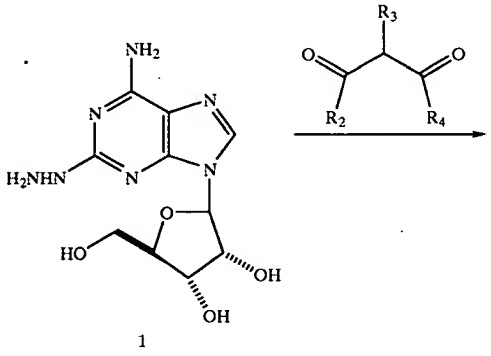
"Alkyl cycloalkyl" denotes the group —R-cycloalkyl where cycloalkyl is a cycloalkyl group and R is a lower alkyl or substituted lower alkyl. Cycloalkyl groups can optionally be unsubstituted or substituted with e.g. halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Alkyl cycloheteroalkyl" denotes the group —R-cycloheteroalkyl where R is a lower alkyl or substituted lower alkyl. Cycloheteroalkyl groups can optionally be unsubstituted or substituted with e.g. halogen, lower alkyl, lower alkoxy, alkylthio, amino, amido, carboxyl, acetylene,

hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

The compounds of this invention can be prepared as outlined in Schemes 1–4. Compounds having the general formula IV can be prepared as shown in Scheme 1.

Scheme 1.



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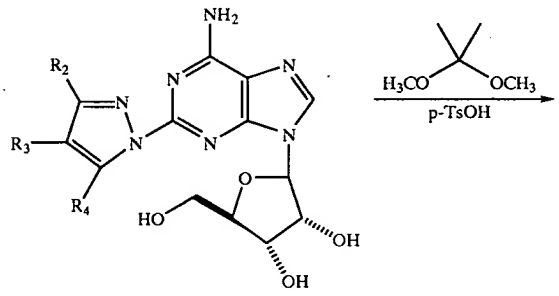

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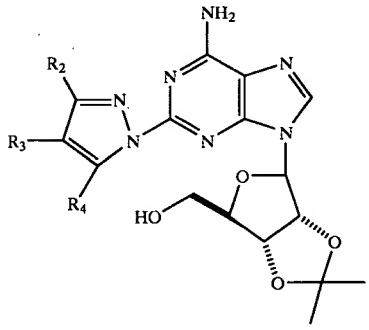

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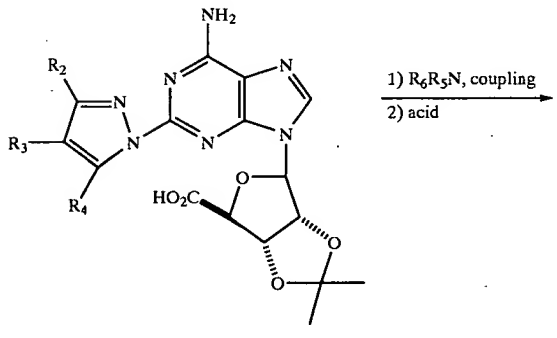

III

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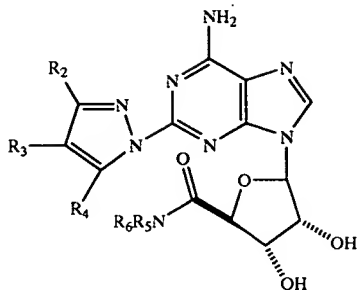
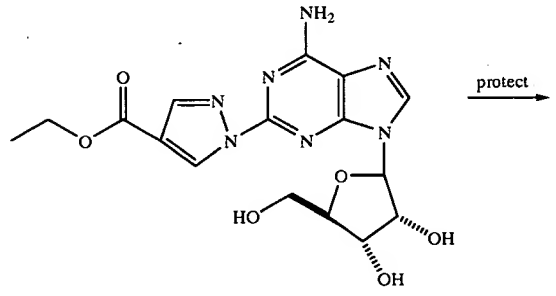


IV

Compound I can be prepared by reacting compound 1 with appropriately substituted 1,3 -dicarbonyl in a mixture of AcOH and MeOH at 80° C. (Holzer et al., J. Heterocycl. Chem. (1993) 30, 865). Compound II, which can be obtained by reacting compound I with 2,2-dimethoxypropane in the presence of an acid, can be oxidized to the carboxylic acid III, based on structurally similar compounds using potassium permanganate or pyridinium chlorochromate (M. Hudlicky, (1990) Oxidations in Organic Chemistry, ACS Monographs, American Chemical Society, Washington D.C.). Reaction of a primary or secondary amine having the formula HNR^6R^7, and compound III using DCC (M. Fujino et al., Chem. Pharm. Bull. (1974), 22, 1857), PyBOP (J. Martinez et al., J. Med. Chem. (1988) 28, 1874) or PyBrop (J. Caste et al. Tetrahedron, (1991), 32, 1967) coupling conditions can afford compound IV.

Scheme 2.



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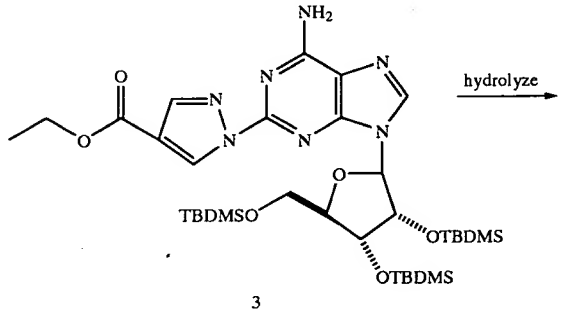

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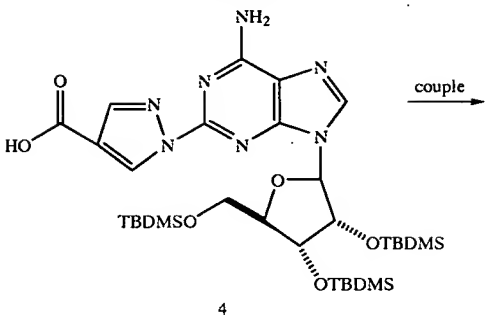

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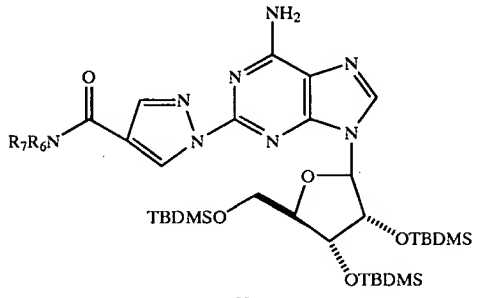

V

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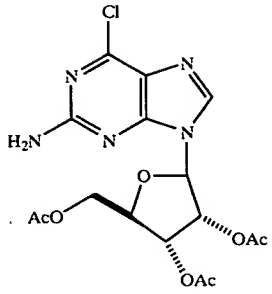

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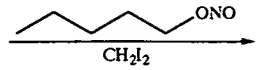

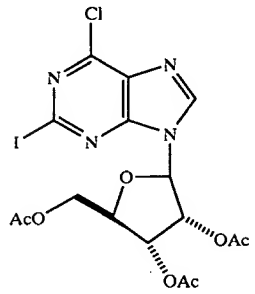

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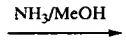
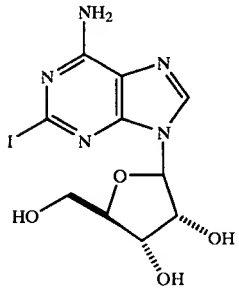


Compound V can be prepared as shown in Scheme 2. The Tri TBDMS derivative 4 can be obtained by treating compound 2 with TBDMSCl and imidazole in DMF followed by hydrolysis of the ethyl ester using NaOH. Reaction of a primary or secondary amine with the formula HNR^6R^7, and compound 4 using DCC (M. Fujino et al., Chem. Pharm. Bull. (1974), 22, 1857), PyBOP (J. Martinez et al., J. Med. Chem. (1988) 28, 1874) or PyBrop (J. Caste et al. Tetrahedron, (1991), 32, 1967) coupling conditions can afford compound V.



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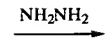
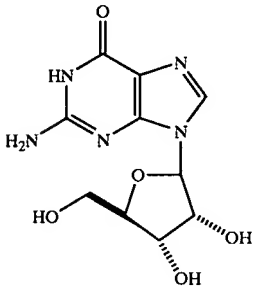


Scheme 3



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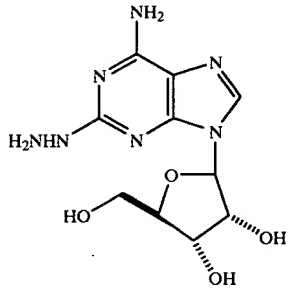

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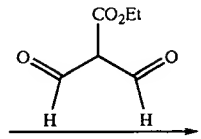

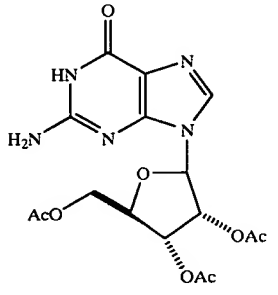

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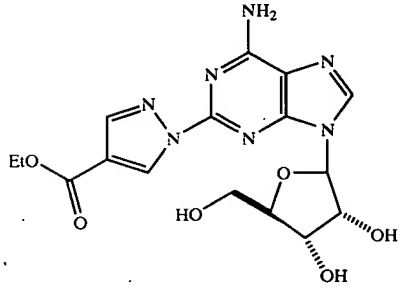

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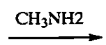

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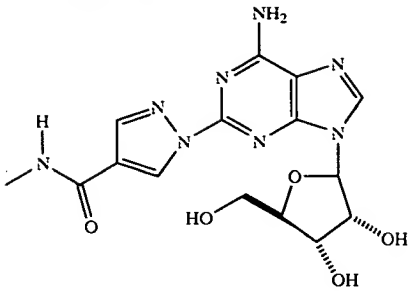
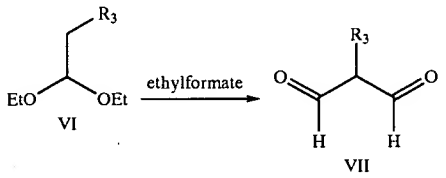


11

A specific synthesis of compound 11 is illustrated in Scheme 3. Commercially available guanosine 5 was converted to the triacetate 6 as previously described (M. J. Robins and B. Uznanski, Can. J. Chem. (1981), 59, 2601–2607). Compound 7, prepared by following the literature procedure of Cerster et al. (J. F. Cerster, A. F. Lewis, and R. K. Robins, Org. Synthesis, 242–243), was converted to compound 9 in two steps as previously described (V. Nair et al., J. Org. Chem., (1988), 53, 3051–3057). Compound 1 was obtained by reacting hydrazine hydrate with compound 9 in ethanol at 80° C. Condensation of compound 1 with ethoxycarbonylmalondialdehyde in a mixture of AcOH and MeOH at 80° C. produced compound 10. Heating compound 10 in excess methylamine afforded compound 11.

Scheme 4



The synthesis of 1,3-dialdehyde VII is described in Scheme 4. Reaction of 3,3-diethoxypropionate or 3,3-diethoxypropionitrile or 1,1-diethoxy-2-nitroethane VI (R_3= CO_2R, CN or NO_2) with ethyl or methyl formate in the presence of NaH can afford the dialdehyde VII (Y. Yamamoto et al., J. Org. Chem. (1989) 54, 4734).

Compounds of this invention are useful in conjunction with radioactive imaging agents to image coronary activity. The compounds of this invention are A_{2A} agonists that are believed to provide specific activation of adenosine A_{2A} receptors in the coronary vessels as opposed to adenosine A1 receptors in the atrium and AV-node and/or A_{2B} receptors in peripheral vessels, thus avoiding undesirable side-effects. Upon administration in a therapeutic amount, the compositions of this invention cause coronary blood vessels to vasodilate to induce coronary steal wherein healthy coronary vessels steal blood from unhealthy vessels resulting in lack of blood flow to heart tissues. Lower doses of the A_{2A} agonists may provide beneficial coronary vasodilatation (less severe) in the treatment of chronic CAD.

As A_{2A} agonists, the compositions of this invention are also useful in adjunctive therapy with angioplasty to induce dilation, inhibit platelet aggregation, and as a general anti-inflammatory agent. A_{2A} agonists, such as the compositions of this invention, can provide the therapeutic benefits described above by preventing neutrophil activation (Purinergic Approaches in Experimental Therapeutics K. A. Jacobson and M. F. Jarvis 1997 Wiley, N.Y.). The compounds of this invention are also effective against a condition called no-reflow in which platelets and neutrophils aggregate and block a vessel. As A_{2A} agonists, the compositions of this invention are effective against no-reflow by preventing neutrophil and platelet activation (e.g., they are believed to prevent release of superoxide from neutrophils). As A_{2A} agonists, the compositions of this invention are also useful as cardioprotective agents through their anti-inflammatory action on neutrophils. Thus, in situations when the heart will go through an ischemic state such as a transplant, they will be useful.

This invention also includes pro-drugs of the above-identified A_{2A} agonists. A pro-drug is a drug which has been chemically modified and may be biological inactive at its site of action, but which will be degraded or modified by one or more enzymatic or in vivo processes to the bioactive form. The pro-drugs of this invention should have a different pharmacokinetic profile to the parent enabling improved absorption across the mucosal epithelium, better salt formulation and/or solubility and improved systemic stability. The above-identified compounds may be preferably modified at one or more of the hydroxyl groups. The modifications may be (1) ester or carbamate derivatives which may be cleaved by esterases or lipases, for example; (2) peptides which may be recognized by specific or non specific proteinase; or (3) derivatives that accumulate at a site of action through membrane selection or a pro-drug form or modified pro-drug form, or any combination of (1) to (3) above.

The compositions may be administered orally, intravenously, through the epidermis or by any other means known in the art for administering a therapeutic agents. The method of treatment comprises the administration of an effective quantity of the chosen compound, preferably dispersed in a pharmaceutical carrier. Dosage units of the active ingredient are generally selected from the range of 0.01 to 100 mg/kg, but will be readily determined by one skilled in the art depending upon the route of administration, age and condition of the patient. This dose is typically administered in a solution about 5 minutes to about an hour or more prior to coronary imaging. No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

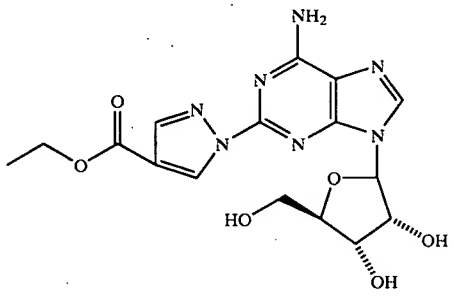
If the final compound of this invention contains a basic group, an acid addition salt may be prepared. Acid addition salts of the compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, maleic, succinic, or methanesulfonic. The hydrochloric salt form is especially useful. If the final compound contains an acidic group, cationic salts may be prepared. Typically the parent compound is treated with an excess of an alkaline reagent, such as hydroxide, carbonate or alkoxide, containing the appropriate cation. Cations such as Na^+, K^+, Ca^{+2} and NH_4^+ are examples of cations present in pharmaceutically acceptable salts. Certain of the compounds form inner salts or zwitterions which may also be acceptable.

Pharmaceutical compositions including the compounds of this invention, and/or derivatives thereof, may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. If used in liquid form the compositions of this invention are preferably incorporated into a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water and buffered sodium or ammonium acetate solution.

Such liquid formulations are suitable for parenteral administration, but may also be used for oral administration. It may be desirable to add excipients such as polyvinylpyrrolidinone, gelatin, hydroxycellulose, acacia, polyethylene glycol, mannitol, sodium chloride, sodium citrate or any other excipient known to one of skill in the art to pharmaceutical compositions including compounds of this invention. Alternatively, the pharmaceutical compounds may be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline, alcohols and water. Solid carriers include starch, lactose, calcium sulfate, dihydrate, teffa alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glycerol monostearate or glycerol distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 gram per dosage unit. The pharmaceutical dosages are made using conventional techniques such as milling, mixing, granulation, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly or filled into a soft gelatin capsule. It is preferred that the compositions of this invention are administered as a solution either orally or intravenously.

The Examples which follow serve to illustrate this invention. The Examples are intended to in no way limit the scope of this invention, but are provided to show how to make and use the compounds of this invention. In the Examples, all temperatures are in degrees Centigrade.

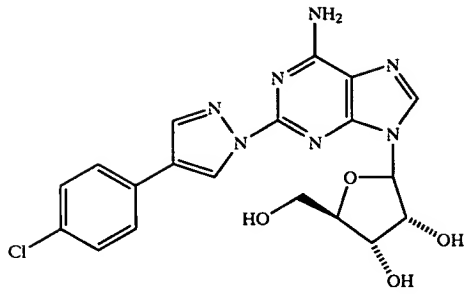
EXAMPLE 1



Ethyl 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2 -yl}pyrazole-4-carboxylate which can also be identified as 2-(4-ethoxycarbonylpyrazol-1-yl) adenosine (12)

To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added (ethoxycarbonyl)malondialdehyde ((0.019 g, 0.12 mmol) and the mixture was heated [heated] at 80° C. for 3 h. The precipitate formed was collected by filtration and washed with EtOH and ether to afford 12. ^{1}HNMR (DMSO-d6) δ1.25 (t, 3 H), 3.5 (m, 1 H), 3.6 (m, 1 H), 3.8 (d, 1 H), 4.15 (d, 1 H), 4.55 (m, 1H), 5.0 (t, 1 H), 5.2 (d, 1 H), 5.5 (d, 1 H), 5.9 (d, 1H), 7.15–7.3 (m, 5 H), 7.8 (br s, 2 H), 8.1 (s, 1H), 8.4 (s, 1 H), 8.9 (s, 1H).

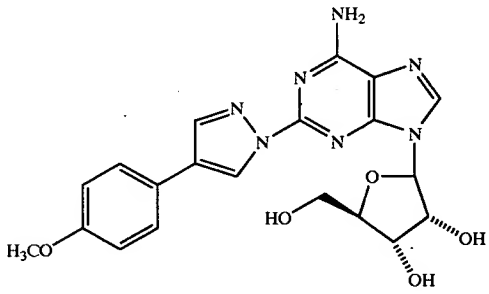
EXAMPLE 2



(4S,2R,3R,5R)-2-{6-amino-2-[4-(4-chlorophenyl) pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3, 4-diol which can also be identified as 2-[4-(4-chlorophenyl)pyrazol-1-yl)]adenosine (13)

To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added 2-(4-chloro)malondialdehyde (0.022 g, 0.12 mmol) and the mixture was heated at 80° C. for 3 h. The precipitate formed was collected by filtration and washed with EtOH and Ether to afford 13. ^{1}HNMR (DMSO-d6) δ3.5 (m, 1 H), 3.6 (m, 1 H), 3.8 (d, 1 H), 4.15 (d, 1 H), 4.2 (q, 2 H), 4.55 (m, 1H), 5.9 (d, 1H), 7.45 (d, 2 H), 7.75 (d, 2 H), 8.25 (s, 1H), 8.35 (s, 1 H), 8.9 (s, 1H).

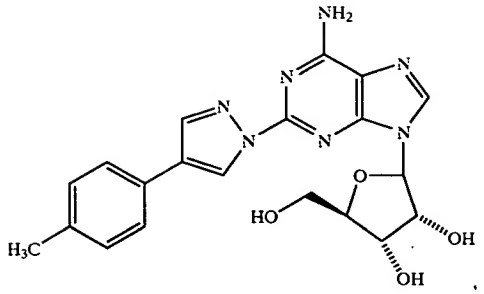
EXAMPLE 3



(4S,2R,3R,5R)-2-{6-amino-2-[4-(4-methoxyphenyl) pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3, 4-diol which can also be identified as 2-[4-(4-methoxyphenyl)pyrazol-1-yl)]adenosine (14)

To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added 2-(4-methoxy)malondialdehyde (0.022 g, 0.12 mmol) and the mixture was heated at 80° C. for 3 h. The precipitate formed was collected by filtration and washed with EtOH and Ether to afford 14. ^{1}HNMR (DMSO-d6) δ3.55 (m, 1 H), 3.65 (m, 1 H), 3.75 (s, 3 H), 3.9 (d, 1 H), 4.15 (d, 1 H), 4.6 (m, 1 H), 5.9 (d, 1 H), 6.75 (d, 2 H), 7.6 (d, 2 H), 8.15 (s, 1H), 8.35 (s, 1 H), 8.8 (s, 1 H).

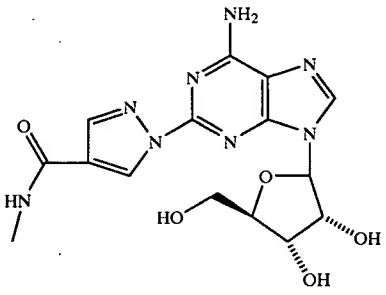
EXAMPLE 4



(4S,2R,3R,5R)-2-{6-amino-2-[4-(4-methylphenyl) pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3, 4-diol which can also be identified as 2-[4-(4-methylphenyl)pyrazol-1-yl)]adenosine (15)

To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added 2-(4-methyl)malondialdehyde (0.019 g, 0.12 mmol) and the mixture was heated at 80° C. for 3 h. The precipitate formed was collected by filtration and washed with EtOH and Ether to afford 15. ^{1}HNMR (DMSO-d6) δ3.55 (m, 1 H\), 3.65 (m, 1 H), 3.75 (s, 3 H), 3.9 (d, 1 H), 4.15 (d, 1 H), 4.6 (m, 1 H), 5.9 (d, 1 H), 6.75 (d, 2 H), 7.6 (d, 2 H), 8.15 (s, 1 H), 8.35 (s, 1 H), 8.8 (s, 1 H).

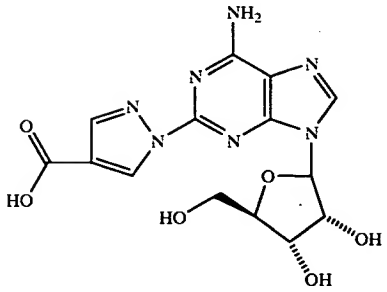
EXAMPLE 5



(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2 - yl}pyrazol-4N-methylcarboxamide which can also be identified as 2-(4-methylaminocarbonylpyrazol-1-yl)adenosine (16)

The mixture heated at 65° C. in for 24 h. After concentration in vacuo, the residue was purified using prep. TLC (10% MeOH:DCM). ^{1}HNMR (CD_3OD) δ2.90 (s, 3 H), 3.78 (m, 1 H), 3.91 (m, 1 H), 4.13 (d, 1 H), 4.34 (d, 1 H), 4.64 (m, 1 H), 6.06 (d, 1 H), 8.11 (s, 1 H), 8.38 (s, 1 H), 9.05 (s, 1 H).

EXAMPLE 6



1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylic acid which can also be identified as 2-(4-carboxypyrazol-1-yl)adenosine (17)

Compound 12 (0.05 mg, 0.12 mmol) was dissolved one equivalent of 1N NaOH. The solution was allowed to stir at Rt for 2 h, then acidified to pH 4. The resulting precipitate was filtered and washed with water and ether. ^{1}HNMR (CD_3OD) Δ3.75 (m, 1 H), 3.90 (m, 1 H), 4.13 (d, 1 H), 4.43 (d, 1 H), 4.64 (m, 1H), 6.05 (d, 1H), 8.10 (s, 1H), 8.35 (s, 1 H), 9.05 (s, 1 H).

EXAMPLE 7

Compositions of this invention were assayed to determine their affinity for the A2A receptor in a pig striatum membrane prep. Briefly, 0.2 mg of pig striatal membranes were treated with adenosine deaminase (2 U/ mL) and 50 mM Tris buffer (pH=7.4) followed by mixing. To the pig membranes was added 2 μL of serially diluted DMSO stock solution of the compounds of this invention at concentrations ranging from 10 nM to 100 microM or the control received 2 microL of DMSO alone, then the trotted antagonist ZM 241385 in Tris buffer (50 mM, pH of 7.4) was added to achieve a final concentration of 2 nM . After incubation at 23° C. for 2 h, then the solutions were filtered using a membrane harvester using multiple washing of the membranes (3x). The filter disks were counted in scintillation cocktail to determine the amount of displacement of tritiated ZM displaced by the compositions of this invention. Greater than a 5 point curve was used to generate Ki's. and the number of experiments is indicated in the column marked in Table 1 below.

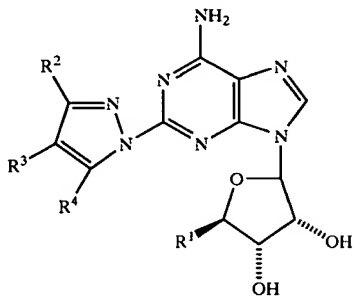
TABLE 1

Compound Number	A_{2a} Ki, nM	n
12	+++	2
13	++	3
14	++	1
15	++	3
16	++	2
17	-	1

+++ = 10–1,000 nM
++ = 1,000–10,000 nM
+ = greater than 10,000 nM
- = greater than 100,000 nM

What we claim is:

1. A compound having the formula:



wherein

R^1 is $—CH_2OH$;

R^2 and R^4 are each hydrogen;

R^3 is selected from the group consisting of CO_2R^{20}, $—CONR^7R^8$ and aryl wherein the aryl substituent is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, C_{1-6} alkyl, CF_3 and OR^{20};

R^7 is selected from the group consisting of hydrogen, C_{1-8} alkyl and aryl, wherein the alkyl and aryl substituents are optionally substituted with one substituent selected from the group consisting of halo, aryl, CF_3, CN, and OR^{20} and wherein each optional aryl substituent is optionally substituted with at least one substituent selected from the group consisting of halo, alkyl, CF_3 CN, and OR^{20};

R^8 is selected from the group consisting of hydrogen and C_{1-8} alkyl; and

R^{20} is selected from the group consisting of hydrogen and C_{1-8} alkyl.

2. The compound of claim 1 wherein R^3 is selected from the group consisting of CO_2R^{20}, $—CONR^7R^8$, and aryl that is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, C_{1-3} alkyl, CF_3 and OR^{20};

R^7 is selected from the group consisting of hydrogen, and C_{1-8} alkyl that is optionally substituted with one substituent selected from the group consisting of halo, CF_3, CN and OR^{20};

R^8 is selected from the group consisting of hydrogen and C_{1-3} alkyl; and

R^{20} is selected from the group consisting of hydrogen and C_{1-4} alkyl.

3. The compound of claim 1 wherein R^3 is selected from the group consisting of CO_2R^{20}, $—CONR^7R^8$, and aryl that is optionally substituted with one substituent selected from the group consisting of halo, C_{1-3} alkyl, and OR^{20};

R^7 is selected from the group consisting of hydrogen, and C_{1-3} alkyl that is optionally substituted with one substituent selected from the group consisting of halo, CF_3, CN and OR^{20};

R^8 is hydrogen; and

R^{20} is selected from the group consisting of hydrogen and C_{1-4} alkyl.

4. The compound of claim 1 wherein R^3 is selected from the group consisting of CO_2R^{20}, $—CONR^7R^8$, and aryl that is optionally substituted with one substituent selected from the group consisting of halo, C_{1-3} alkyl and OR^{20};

R^7 is selected from the group consisting of hydrogen, and C_{1-3} alkyl;

R^8 is hydrogen; and

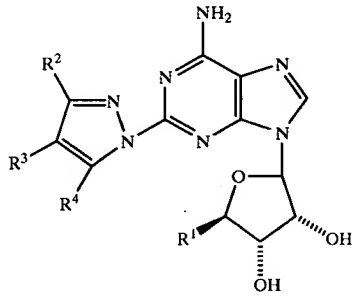
R^{20} is selected from the group consisting of hydrogen and C_{1-4} alkyl.

5. The compound of claim 4 wherein R^7 is a methyl.

6. The compound of claim 4 wherein R^3 is $—CO_2Et$.

7. The compound of claim 1 selected from the group consisting of 2-(4-methylaminocarbonylpyrazol-1-yl) adenosine; 2-(4-ethoxycarbonylpyrazol-1-yl)adenosine; 2-[4-(4-chlorophenyl)pyrazol-1-yl)]adenosine; 2-[4-(4-methoxyphenyl)pyrazol-1-yl)]adenosine; 2-[4-(4-methylphenyl)pyrazol-1-yl)]adenosine; and 2-(4-carboxypyrazol-1-yl)adenosine.

8. A compound having the following formula:



wherein

R^1 is $—CH_{20}OH$;

R^2 and R^4 are each hydrogen;

R^3 is $—CONR^7R^8$;

R^7 is methyl; and

R^8 is hydrogen.

9. A pharmaceutical composition comprising a compound of claim 1 and one or more pharmaceutically acceptable excipients.

10. The pharmaceutical composition of claim 9 wherein the pharmaceutical composition is in the form of a solution.

11. A method for stimulating coronary vasodilation in a mammal by administering to the mammal a therapeutically effective amount of a compound of claim 1 that is sufficient to stress the heart and induce a coronary steal situation for the purposes of imaging the heart.

12. The method of claim 11 wherein the therapeutically effective amount ranges from about 0.01 to about 100 mg/kg weight of the mammal.

13. The method of claim 11 wherein the mammal is a human.

* * * * *

ATTACHMENT B
COPY OF THE CERTIFICATE OF CORRECTION WHICH ISSUED WITH RESPECT TO US PATENT NO. 6,403,567

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

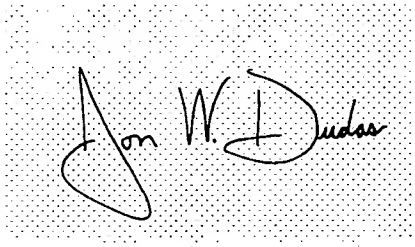
PATENT NO. : 6,403,567 B1
APPLICATION NO. : 09/338185
DATED : June 11, 2002
INVENTOR(S) : Zablocki et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 20,
Line 37, delete "-$CH_{20}OH$" and replace with -- -CH_2OH --.

Signed and Sealed this

Twentieth Day of June, 2006



JON W. DUDAS
Director of the United States Patent and Trademark Office

ATTACHMENT C
NOTICE OF RECORDATION AND ASSIGNMENT FROM THE INVENTORS TO CV THERAPEUTICS, INC.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

OCTOBER 26, 1999

PTAS

MCDONNELL, BOEHNEN, HULBERT & BERGHOFF
A. BLAIR HUGHES
300 SOUTH WACKER DRIVE - 32ND FLOOR
CHICAGO, IL 60606

101120687A

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 08/16/1999

REEL/FRAME: 010187/0341
NUMBER OF PAGES: 4

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
ZABLOCKI, JEFF A.

DOC DATE: 06/29/1999

ASSIGNOR:
ELZEIN, ELFATIH O.

DOC DATE: 07/06/1999

ASSIGNOR:
PALLE, VENKATA P.

DOC DATE: 07/06/1999

ASSIGNEE:
CV THERAPEUTICS, INC.
3172 PORTER DRIVE
PALO ALTO, CALIFORNIA 94304

SERIAL NUMBER: 09338185
PATENT NUMBER:

FILING DATE: 06/22/1999
ISSUE DATE:

ENTERED

LAWAN FLETCHER, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

08-18-1999

101120687

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AUG 16

FORM PTO-1595 (8-98) OMB 0651-0011

Docket No. 99,423

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

RECORDATION FORM COVER SHEET

To The Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
   Jeff A. Zablocki
   Elfatih O. Elzein
   Venkata P. Palle

   Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)

   Name: CV Therapeutics, Inc.

   Address: 3172 Porter Drive

   City: Palo Alto State: California

   Country: U.S.A. Zip: 94304

   Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:

   ☒ Assignment ☐ Merger

   ☐ Security Agreement ☐ Change of Name

   ☐ Other _____

   Execution Date: 6/29/99 and 7/6/99

4. Application number(s) or patent number(s):

   If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)	Filing Date	B. Patent No.(s)
09/338,185	June 22, 1999	

   Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

   Name: A. Blair Hughes

   Registration No.: 32,901

   Company Name: McDonnell, Boehnen, Hulbert & Berghoff

   Street Address: 300 South Wacker Drive – 32nd Floor

   City: Chicago State: Illinois

   Country: U.S.A. ZIP: 60606

6. Total number of applications and patents involved: 1

7. Total Fee (37 CFR 3.41)..... $40.00

   ☒ Enclosed

   ☐ Authorized to be charged to deposit account

8. Deposit account number:

   13-2490

08/18/1999 MTHAI1 00000082 09338185
01 FC:581 40.00 OP

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9. Statement and signature.
   To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

A. Blair Hughes		Date: August 11, 1999
Printed Name of Person Signing	Signature	

Total number of pages including cover sheet, attachments, and document: 4

Mail documents to be recorded with required cover sheet information to:

Commissioner of Patents and Trademarks
Box Assignments
Washington, D.C. 20231

ASSIGNMENT

Case No.: 99,423
Serial No.: 09/338,185
Inventors: Jeff A. Zablocki, Elfatih O. Elzein and Venkata P. Palle
Date of Execution of Application: 6/29/99 and 7/6/99
Filing Date: 6/22/99

In consideration of One Dollar ($1.00) and other good and valuable considerations in hand paid, the receipt and sufficiency whereof are hereby acknowledged, the undersigned hereby assign to:

CV Therapeutics, Inc.

its successors and assigns, the entire right, title and interest in the invention or improvements of the undersigned disclosed in an application for Letters Patent of the United States, entitled:

N-PYRAZOLE A_{2A} RECEPTOR AGONISTS

and identified as:

Case No. 99,423

in the offices of McDONNELL BOEHNEN HULBERT & BERGHOFF and in said application and any and all other applications, both United States and foreign, which the undersigned may file, either solely or jointly with others, on said invention or improvements, and in any and all Letters Patent of the United States and foreign countries, which may be obtained on any of said applications, and in any reissue or extension of such patents, and further assigns to said assignee the priority right provided by the International Convention.

The undersigned hereby authorize and request the Commissioner of Patents and Trademarks to issue said Letters Patent to said assignee.

The undersigned hereby authorize and request the attorneys of record in said application to insert in this assignment the filing date and serial number of said application when officially known, and the date of execution of the application.

The undersigned warrant themselves to be the owners of the entire right, title and interest in said invention or improvements and to have the right to make this assignment, and further warrant that there are no outstanding prior assignments, licenses, or other encumbrances on the interest herein assigned.

For said considerations the undersigned hereby agree, upon the request and at the

McDONNELL BOEHNEN
HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001

expense of said assignee, its successors and assigns, to execute any and all divisional, continuation and substitute applications for said invention or improvements, and any necessary oath, affidavit or declaration relating thereto, and any application for the reissue or extension of any Letters Patent that may be granted upon said application and any and all applications and other documents for Letters Patent in foreign countries on said invention or improvements, that said assignee, its successors or assigns may deem necessary or expedient, and for the said considerations the undersigned authorize said assignee to apply for patents for said invention or improvements in its own name in such countries where such procedure is proper and further agree, upon the request of said assignee, its successors and assigns, to cooperate to the best of the ability of the undersigned with said assignee, its successors and assigns, in any proceedings or transactions involving such applications or patents, including the preparation and execution of preliminary statements, giving and producing evidence, and performing any and all other acts necessary to obtain, maintain and enforce said Letters Patent, both United States and foreign, and vest all rights therein hereby conveyed in the assignee, its successors and assigns, whereby said Letters Patent will be held and enjoyed by the said assignee, its successors and assigns, to the full end of the term for which said Letters Patent will be granted, as fully and entirely as the same would have been held and enjoyed by the undersigned if this assignment had not been made.

WITNESS my hand and seal this 29th day of June, 1999.

Jeff A. Zablocki

Jeff A. Zablocki

State of California

County of Santa Clara

The foregoing instrument was acknowledged before me this 29th day of June, 1999 by Jeff A. Zablocki

ESI1 TANA ROLL COMM. #1207870 Notary Public-California SANTA CLARA COUNTY My Comm. Exp. Jan. 11, 2003 ESI1

Tana Roll

NOTARY PUBLIC

McDONNELL BOEHNEN
HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 913-0001

WITNESS my hand and seal this 6th day of July, 1999.

Elfaith Elzein
Elfaith O. Elzein

State of California

County of Santa Clara

The foregoing instrument was acknowledged before me this 6th day of July, 1999 by Elfaith O. Elzein

TANA ROLL
COMM. #1207870
Notary Public-California
SANTA CLARA COUNTY
My Comm. Exp. Jan. 11, 2003
ESI1

Tana Roll
NOTARY PUBLIC

WITNESS my hand and seal this 6th day of July, 1999.

P.V.P.P. Acharyulu
Venkata P. Palle

State of California

County of Santa Clara

The foregoing instrument was acknowledged before me this 6th day of July, 1999 by Venkata P. Palle

TANA ROLL
COMM. #1207870
Notary Public-California
SANTA CLARA COUNTY
My Comm. Exp. Jan. 11, 2003
ESI1

Tana Roll
NOTARY PUBLIC

McDONNELL BOEHNEN
HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
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FORM PTO-1595

Docket No. 99,423

RECORDATION FORM COVER SHEET
PATENTS ONLY

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Patent and Trademark Office

To The Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Jeff A. Zablocki
Elfatih O. Elzein
Venkata P. Palle

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)

Name: CV Therapeutics, Inc.

Address: 3172 Porter Drive

City: Palo Alto State: California

Country: U.S.A. Zip: 94304

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AUG 16 1999

3. Nature of conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other _____

Execution Date: 6/29/99 and 7/6/99

Additional name(s) & address(es) attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)	Filing Date	B. Patent No.(s)
09/338,185	June 22, 1999	

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: A. Blair Hughes

Registration No.: 32,901

Company Name: McDonnell, Boehnen, Hulbert & Berghoff

Street Address: 300 South Wacker Drive – 32nd Floor

City: Chicago State: Illinois

Country: U.S.A. ZIP: 60606

6. Total number of applications and patents involved: 1

7. Total Fee (37 CFR 3.41).....$40.00

☒ Enclosed

☐ Authorized to be charged to deposit account

8. Deposit account number:

13-2490

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9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

A. Blair Hughes
Printed Name of Person Signing

C. Blair Hughes
Signature

Date: August 11, 1999

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ATTACHMENT D
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PTO/SB/81 (01-06)
Approved for use through 12/31/2008. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM

Application Number	09/338,185; Patent No. 6,403,567
Filing Date	22 Jun 1999; Issued 11 June 2002
First Named Inventor	Jeff Zablocki
Title	N-Pyrazole A2A Adenosine Receptor Agonists
Art Unit	1623
Examiner Name	CRANE, LAWRENCE E.
Attorney Docket Number	99-0423

I hereby revoke all previous powers of attorney given in the above-identified application.

I hereby appoint:

[X] Practitioners associated with the Customer Number: 27716

OR

[ ] Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please recognize or change the correspondence address for the above-identified application to:

[X] The address associated with the above-mentioned Customer Number:

OR

[ ] The address associated with Customer Number:

OR

[ ] Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

[ ] Applicant/Inventor.

[X] Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Signature		Date	6/3/08
Name	Tricia Suyani	Telephone	(650) 384-8500
Title and Company	Senior Vice President & General Counsel		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[X] *Total of 2 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/96 (01-08)
Approved for use through 05/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: CV Therapeutics, Inc.

Application No./Patent No.: 6,403,567 Filed/Issue Date: 11 June 2002

Entitled: N-Pyrazole A2A Adenosine Receptor Agonists

CV Therapeutics, Inc., a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. [X] the assignee of the entire right, title, and interest; or

2. [ ] an assignee of less than the entire right, title and interest
(The extent (by percentage) of its ownership interest is _____%)

in the patent application/patent identified above by virtue of either:

A. [X] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 010187, Frame 0341, or for which a copy thereof is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[ ] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature	6/3/08 Date
Tricia Suvari	(650) 384-8500
Printed or Typed Name	Telephone Number
Senior Vice President & General Counsel	
Title	